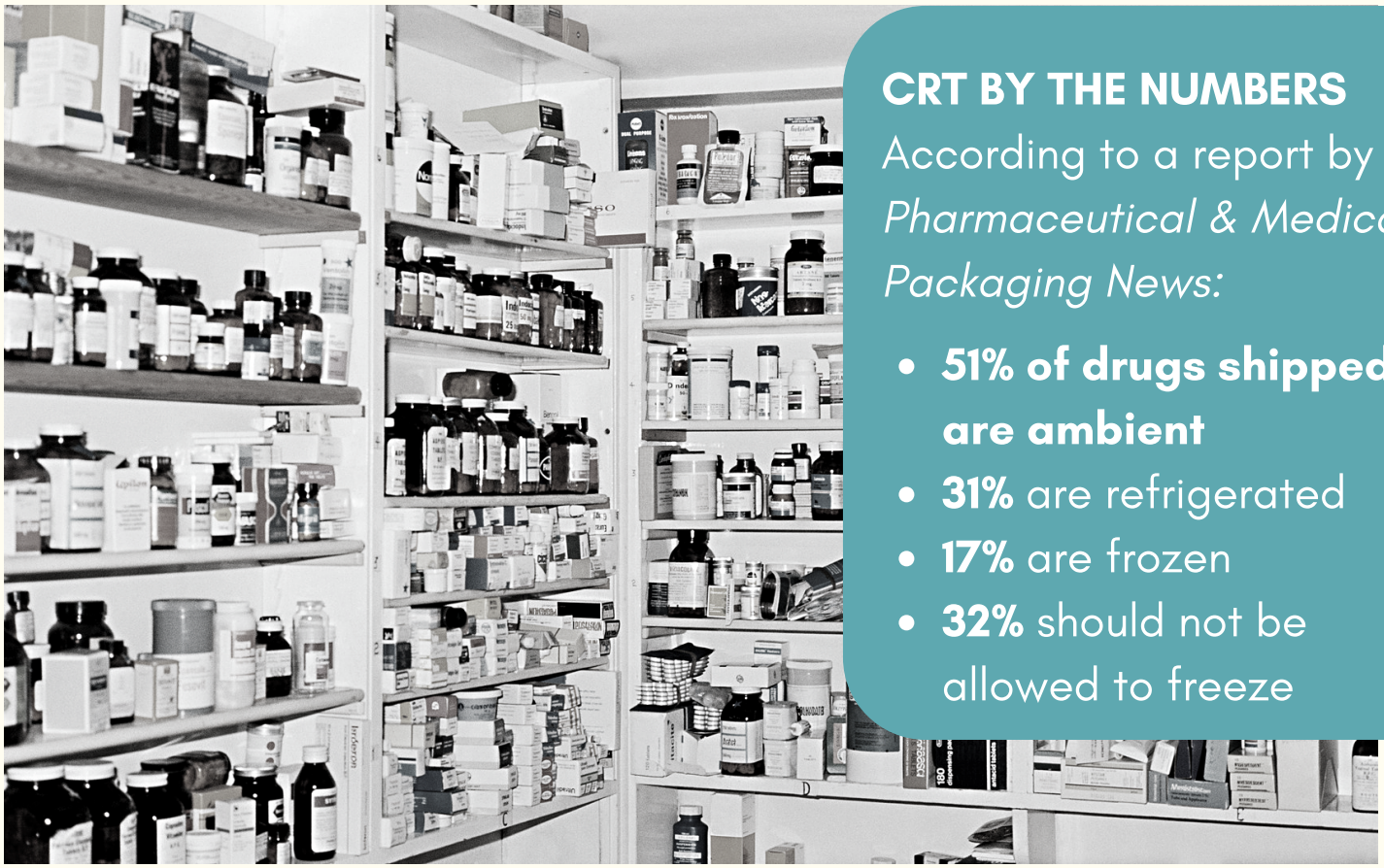
Cold Chain Global Forum
SPRING . 19
Temperature Controlled Life Science Supply Chains

TRANSPORTING **CRT** PRODUCTS

TOP CHALLENGES & SOLUTIONS FOR PROTECTING CONTROLLED ROOM TEMPERATURE PRODUCTS

2019 REPORT



CRT BY THE NUMBERS

According to a report by *Pharmaceutical & Medical Packaging News:*

- **51% of drugs shipped are ambient**
- **31%** are refrigerated
- **17%** are frozen
- **32%** should not be allowed to freeze

We don't have to tell you that effective temperature management is critical for ensuring the safety and effectiveness of all types of drugs, even those that may not classify as "cold chain" products such "ambient" or "room temperature" medicines.

Not too long ago, "ambient," "room temperature" and even "controlled room temperature" (CRT) were considered synonymous and, as they were considered more or less resilient again temperature excursions, were provided little to no thermal protection across the supply chain. However, this is beginning to change. **Increased regulatory focus, an improved understanding of how inappropriate storage conditions impact product integrity and the increased volume of temperature sensitive CRT biosimilars/biologics** have pushed manufacturers to pay just as much attention to room temperature products as they do traditional cold chain drugs.

This being said, transporting room temperature drugs is not without its challenges. Though it may sound counterintuitive, safeguarding room products from temperature excursions can actually be more expensive and difficult than protecting their cooler counterparts. From reasons ranging from costs to simple effectiveness, one simply just can't apply the same solutions and methodologies to ambient products as they do those that require refrigeration.

With this in mind, below we've outlined the key challenges and solutions associated with protecting CRT and ambient drugs across the supply chain.

Challenge #1
Defining Cold Chain Drugs

Though packaging and storage requirements for frozen and refrigerated drugs have pretty much always been clearly defined (between -10°C to -25°C and +8°C to +15°C, respectively), requirements for "ambient" or "room temperature" drugs are notably more ambiguous. Though some regulatory entities offer some guidance on CRT labeling, **the definition of CRT is often entirely dependent on the product being shipped and the length of time it is being shipped for.** To complicate the matter, enforcement of these standards are quite inconsistent; while some customs inspectors or health authorities are rigorous about CRT adherence, others are less so.

Solution #1
Definition Cheat Sheet

Below is a breakdown of global regulatory definitions and guidance for ambient drugs. In summary though, **terms like "ambient", "room temperature" and "cold chain" should be avoided as the only labelling for storage or transport boxes and containers because they are not always clear and might have different meanings in other parts of the world.** Storage conditions should always be explicitly specified in terms of a defined temperature range (e.g., 15°C -25°C or +2°C to +8°C). Particular attention should also be given to avoiding freezing of liquids and semi-solids.

	European Pharmacopoeia (Pharm.Eur.)	WHO	U.S. Pharmacopeia (USP)	Japanese Pharmacopeia (JP)
Room Temp	**15°C – 25°C**	**15°C – 25°C**	temperature prevailing in a work area	**1°C – 30°C**
CRT	-	-	excursions between **15°C and 30°C** are allowed	-
Ambient	-	**15°C – 25°C or 30°C** depending on climatic conditions	-	-

EMA Guidelines on Declaration of Storage Conditions

Testing conditions where the product is stable	**Required Labeling Conditions**	**Additional labeling statement, where relevant**
25°C/60%RH (long term) 40°C/75%RH (accelerated) *or* 30°C/65%RH (long term) 40°C/75%RH (accelerated)	None (*The following PL statement is required:* *This medicinal product does not require any special storage conditions.*)	Do not refrigerate or freeze
25°C/60%RH (long term) 30°C/60 or 65%RH (intermediate) or 30°C/65%RH (long term)	Do not store above 30°C *or* Store below 30°C	Do not refrigerate or freeze
25°C/60%RH (long term)	Do not store above 25°C or Store below 25°C	Do not refrigerate or freeze

**definitions sourced from What are the regulatory Definitions for "Ambient", "Room Temperature" and "Cold Chain"?*
https://www.gmp-compliance.org/gmp-news/what-are-the-regulatory-definitions-for-ambient-room-temperature-and-cold-chain

Solution #2

Know Your Product

Tighten up the data and procedures for determining the **stability budget** of pharma products to ensure accuracy. Temperature ranges permitted during pharmaceutical product distribution, as well as the labeled storage conditions, are inseparably linked to stability data for each product so "obtaining a clear understanding of the product's true storage and shipping temperature range is paramount to the stability of that product," Steve Winyard, Portfolio Manager – Life Sciences at Inmark, told Pharma IQ in 2018. "If a product is being shipped internationally by air transport over two or more days, the packaging requirements would be quite different than if it were shipped domestically using a same or next day delivery service."

In an article published in **WorldPharma**, Russell Brierley, Lupin's Director of Clinical Supplies, advises companies to create excursion profile with their quality group that predefines several levels of excursion to allow timely dispensation of any shipments that have temperature excursions:

- Level 1: No temperature excursion, the drug is maintained at its labelled storage condition
- Level 2: The acceptable temperature excursions that do not need any follow-up investigation
- Level 3: The temperature excursions that might consider some quality input or investigation
- Level 4: The temperature excursions where products should be rejected

Solution #3

Know Your Trade Lane

Understanding the likely ambient thermal profile of transit lanes as well as any potential factors (such as hand-offs or check points) that could delay the shipment or result in temp excursions is critical for effectively determining thermal protection and packaging requirements for your product. Where is your product going? Take a look at the full end-to-end journey and, at each touchpoint, evaluate local temperatures, taking into account annual and seasonal average minimum and maximum extreme temperatures, as well as the potential package exposure time associated with that touchpoint.

According to **Geoffrey Glauser, Senior Consultant, Conceptual Mindworks Inc.**, at a minimum, your Lane Characterization process should include:

- Name and address of the sending site
- Name and address of the receiving site
- Quantity of material being shipped
- Product name and labeled storage conditions
- All transport service providers, including trucking companies, airlines, and ocean transport services
- Identification of the touchpoints within the lane
- Identification of all product handoffs
- Annual average minimum and maximum temperature extremes at the sending and receiving sites as well as at all touchpoints within the lane
- Duration of transport between each touchpoint

Solution #4

Invest in Technology

Leading-edge companies are leveraging electronic monitoring and reporting equipment, ranging from throwaway sensors to elaborate global communications networks, to track shipments by geography and by environmental conditions. As a result, logistics providers are now capable of providing near-real-time monitoring of shipment temperatures, from the warehouse to the loading docks of pharmacies and hospitals. The data collected through these sensors can also help develop improved predictive models for future shipments. In fact, according to our 2018 Industry **Survey, over 75% of our respondents were looking to invest in temperature monitoring devices in the near future.**

Challenge #2
Controlling Costs

When the **EU GDP standards** were established in 2013 expanding temperature-control compliance requirements to CRT products, the first reaction of many companies was to apply the same technology as refrigerated containers—insulated boxes with gel packs. However, not only is it more difficult to keep a product at room temperature (*because of the mass of PCM material necessary*) than a refrigerated product, (*whose PCM can pack more cooling into a given mass*), it can also bbe significantly more expensive**.** Considering that, at least according to some estimates , **90-93% of drugs in the market are CRT** (10X the size of the cold chain market), if companies were to leverage the same insulation solutions, technical practices and devices to transport CRT drugs that they use for cold chain products, the cost would be staggering.

Pharmaceutical Commerce's Sourcebook estimates that logistics costs for cold chain drugs will increase to *$16.6 billion by 2021, 24% higher than they were in 2017*. As they explain, part of this growth will be due to increased spending on CRT shipping. In fact, logistics providers are beginning to receive more requests for Controlled Room Temperatures (CRT) which include the use of insulated containers, refrigerants, thermal blanketing, and temperature-monitoring electronics. In addition, 2019 Cold Chain Global Forum speaker Vadim Klyushnichenko, VP Pharmaceutical Development and Quality, California Institute for Biomedical Research, told us that their CRT logistics costs have gone up by as much as 10% over the past year.

Though there is a trend toward more spending on devices and system for controlled room temperature (CRT) shipping, to date, most of this involves more careful monitoring of shipping conditions, and greater use of temperature-controlled transport vehicles, and not necessarily extensive use of insulation or other environmental controls, according to the 2017 Pharmaceutical Commerce's Sourcebook.

So how are leading-edge companies protecting CRT products without breaking the bank?

Solution #1

Passive Containers & Thermal Blankets

Considering a deploying a single refrigerated truck can cost about $60K, many supply chain leaders are turning towards more simple and cost-effective solutions such as thermal blankets and passive containers for CRT shipments.

Both thermal blankets and standard insulated containers offer multi-tiered and customizable insulation and protection from temperature excursions. As an added bonus, since many of these solutions can be re-used, they have the potential to deliver long-term value. Though they might not be appropriate for products with tighter stability budgets or for long journeys through extreme temperature, they do offer a viable alternative to more resource heavy transportation options.

Solution #2

Know Your Product Part II

After years of actively collecting data around this issue, the industry has a better understanding the stability of time and temperature-sensitive drug products than ever before. In many cases, they're finding that products are more thermally robust than previously thought. In fact, the current USP temperature range for CRT is very narrow and does not take into account expanded drug product stability data. Unfortunately, this tight temp range can lead to perceived shipping excursions, costly investigative responses and the unnecessary disposal of viable products.

To combat this issue, aim to generate stability data that can support labeling products with a wide temperature range that encompasses typical excursions encountered when shipping products, including pharmacy mail order distribution and the patient in-use period. USP also recommends that both the primary packaging and the case labels list both the storage conditions (and distribution conditions if different) and typical excursion temperature data (i.e. store below 30°, excursion to 40° for 1 month).

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Learn more about safely and cost-effectively transporting CRT products at the 2019 Cold Chain Global Forum Spring!

8:00am on Monday, June 10, 2019

WORKSHOP A: Looking Beyond the Cold Chain: Preparing your Supply for Increased Vigilance of CRT Products

With regulators across the globe becoming increasingly interested in how organizations are controlling the variables when distributing CRT/Ambient products, companies must re-assess their processes to ensure compliance. Even if total temperature monitoring is not required by regulators, it is crucial to show that you have strong processes in place to stay off their radar. Regulators want to see that you have your documentation in order for these products and have a full understanding of your transport process.

From this workshop you will walk away with insight on how to:

- Calculate accurate temperature profiles for ambient products and properly analyze data collected
- Understand the environment where your products will be traveling and how to best control the elements
- Define your routes through qualification & validation of shipping lanes and profiling using historical data
- Pinpoint the packaging required to seamlessly ship ambient products globally and where a more custom design is needed
- Discuss the global GDP landscape for CRT products and where your products get flagged more often

Vadim Klyushnichenko, Ph.D.
VP Pharmaceutical Development and Quality
California Institute for Biomedical Research (Calibr), The Scripps Research Institute (TSRI)

1:15pm on Tuesday, June 11, 2019

USP Update on Storage and Transportation Practices to Include Risk Identification and Mitigation with a Special Focus on Excursion Management and the Proper and Improper Use of Mean Kinetic Temperature

This presentation will review the USP Packaging and Distribution Expert Committee's work on USP General Chapter <1079> Good Storage and Shipping Practices for Drug Products moving to a Risk Mitigation Chapter to include a high-level overview of comments submitted to the draft being publish in the Pharmacopeial Forum.

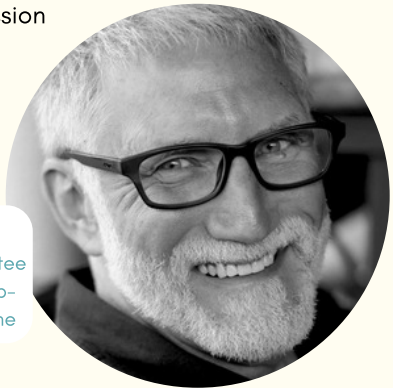
Discussion and example of proper and improper use of Mean Kinetic Temperature for storage and excursion management for temperature controlled pharmaceuticals. Mean Kinetic Temperature (MKT) has been around for many years, but its use has not been consistent. We will look at examples of how MKT should not be used as well as supported methods.

The discussion will also focus on USP <659> Packaging and Storage Requirements, specifically the definitions around Controlled Room Temperature (CRT) and Controlled Cold Temperature (CC), excursion management, and the uses of MKT for both.

- Focus on the use of a USP Risk Mitigation Chapter for the Storage and Transportation of Finished Drug Products
- Review of USP storage requirements for Controlled Room Temperature and Controlled Cold Product.
- Review MKT and its proper and improper use with examples for discussion

Chris J. Anderson
Director, Quality System
Cardinal Health

Member of the United States Pharmacopeia (USP) Packaging and Distribution Expert Committee Co-Chair of the USP <1079> Sub-Committee, and a member of the Repackaging Sub-Committee



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