PHARMACEUTICAL TEMPERATURE MONITORING: ADAPTING YOUR BUSINESS FOR SUCCESS

A WHITE PAPER

Correspondence should be addressed to:
Josh Griggs, Director of Sales - Healthcare and National Accounts; SmartSense;
11001 Bren Road E, Minnetonka, MN 55343; 1-866-806-2653; josh.griggs@digi.com

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Introduction: The Product Viability of Pharmaceuticals

There's a chain of responsibility that comes into play when proper storage of pharmaceutical products is on the line. Product viability ensures the intended effectiveness of the product, which then maximizes the health and well-being of the recipient or the consumer. The integrity of many products can be affected if left outside room temperature, while others can risk consumer safety if not properly—and consistently—refrigerated.

The product viability of pharmaceuticals starts at the source. All suppliers have an obligation to ensure proper storage conditions at their sites and to ensure that shipping processes maintain product integrity throughout product receipt by health care professionals. Those health care professionals must then ensure that proper storage conditions are maintained until the products are dispensed and/or administered to patients. With so many crucial steps between creation and administration of pharmaceutical products, true safety and integrity can only be accomplished through proper temperature monitoring. The proliferation of products that require cold chain management makes it incumbent upon the supplier to maintain the cold chain process at their sites and through delivery, and for the health care professional to properly receive and constantly monitor temperature integrity prior to administration or delivery to the patient.

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Part I: The Complex World of Pharmaceutical Temps

All pharmaceutical products have temperature storage requirements that can be found on their product packaging. Products with no visible instructions are allowed to be stored at room temperature, the understood requirement here being that anything warmer than room temperature could impact potency. All pharmaceutical products also have a listed expiration date. If products are stored outside of their temperature range, their viability can be affected and, even if still viable, may shorten the expiration date of the product, often substantially.

Many pharmaceutical products have a "controlled room temperature" storage requirement. The United States Pharmacopeia[1] defines that "controlled room temperature" indicates a temperature maintained thermostatically that encompasses the usual and customary working environment of 20°C to 25°C (68°F to 77°F), that results in a mean kinetic temperature calculated to be not more than 25°C, and that allows for excursions between 15°C to 30°C (59°F to 86°F) that are experienced in pharmacies, hospitals, and warehouses.[1]

Imagine if the air conditioning wasn't functional for several days in the heat of summer. Could we be certain that the excursion didn't not go over 86°F for these products? If it did, for how long and at what range of temperatures?

The Effects of Extreme Temperatures

Many common medications can break down in temperature conditions beyond the excursion range. Here are some pretty common examples for modern consumers:

- Hydrocortisone and other creams may separate in extreme heat.
- Gel capsules may become sticky, clump together, and break down in severe heat.
- Studies suggest that when stored above 98°F, lorazepam and diazepam may decrease in potency by 75% and 25%, respectively.[2]
- Thyroid hormones can be sensitive to extreme heat. Due to the narrow therapeutic range of these products, that's of special concern for patients.
- Other hormone preparations, such as birth control pills, can also be affected by extreme heat.

Extreme cold can be just as detrimental for other life-saving drugs. If the heat fails in the dead of winter, can we be certain that an excursion hasn't occurred at the lower end of the permissible range?

For example:

- Insulin should never be used if it's been frozen.
- Many vaccines—such as hepatitis A and B, HPV, and tetanus-containing vaccines—can be damaged if exposed to frozen temperatures.[3]

We've seen a proliferation of pharmaceuticals that have cold storage requirements, meaning they must be refrigerated or frozen and then maintained at the proper temperature range. For one, the varicella and zoster vaccines currently available require that they be stored in a freezer. Refrigeration-specific products that immediately

come to mind are insulins and vaccines, but they're not alone. Other drugs that must be stored in the refrigerator, according to the Therapeutic Research Center[4], include:

- Injectable drugs such as adalimumab (Humira) and epoetin alfa (Epogen, etc [U.S.]; Eprex [Canada])
- Oral drugs such as ritonavir capsules (Norvir) and sirolimus oral solution (Rapamune)
- Ophthalmic drugs such as azithromycin (AzaSite [U.S. only]) and latanoprost (Xalatan)
- Nasal drugs such as calcitonin (Miacalcin, Fortical [U.S.]; Calcimar [Canada])
- Drugs for inhalation through a nebulizer such as arformoterol (Brovana [U.S. only]) and formoterol (Perforomist [U.S. only])
- Suppositories such as promethazine (U.S.)

Refrigerator temperature is defined as between 2°C to 8°C (36°F to 46°F). This will help ensure an average refrigerator temperature of 5°C (40°F). Freezer temperature is defined as between -25°C to -15°C (-13°F to 14°F). With such small ranges to work with, these products understandably pose additional challenges to proper storage. Many refrigerated and frozen pharmaceuticals can become unusable if excursions occur, or may have markedly reduced expiration dates, if usable.

- Neupogen is stable at room temperature for only 24 hours.[5]
- Copaxone is stable for only 1 month at room temperature.[6]
- Avonex prefilled syringes are stable for 7 days at room temperature.[7]
- Virtually all insulin formulations are only good for a defined period when stored at room temperature. Many insulin products are only good for 28 to 31 days when stored at room temperature, but are viable through the expiration date when stored at the proper temperature range in a refrigerator.[8]
- Frozen herpes zoster vaccine has a shortened expiration date when left unfrozen for given periods of time, based on manufacturer's guidance.

Temperature Knowledge Is Power

For both ambient controlled room temperature and for the cold storage of pharmaceuticals, it's vital to know that products are being maintained at the proper temperatures, especially when so many products have temperature-sensitive stability.

There are myriad factors to consider in the cold storage area. Understanding product viability when improperly stored for a period of time is one issue, but ask yourself:

- Are your refrigerator and freezer units maintaining proper temperature ranges at all times? How can you be certain that this is happening?
- What happens to the products contained in a refrigerator or freezer during equipment failure or a power outage?
- Are defrost cycles creating variations in temperatures beyond excursion ranges?

Product viability can often only be determined by the manufacturer of the product, if you can accurately provide the variations in temperature and the duration of these variations during an excursion. This has led, and rightfully so, to an increased focus on the process of properly monitoring these temperatures to maintain product integrity and to understand the cause, duration, and the temperature range of an excursion.

Part II: Changing Storage and Temperature Standards

Born from research and guidance by manufacturers, the CDC, and other government agencies throughout the years, temperature storage standards have become more defined. If you store products with more sensitivity to temperature excursions in your refrigerator and freezer along with less sensitive products, then your standards have to be set to those products with the greatest amount of sensitivity to excursions. Ambient temperature must also be carefully monitored so that room temperature requirements are met.

Vaccines are one class of temperature-sensitive products where there's been a great deal of guidance on storage and temperature monitoring. The Center for Disease Control (CDC) has redefined and refined the requirements for storing vaccines several times in recent years, and proper storage of vaccines based on CDC guidelines is a necessity to participate in the federal Vaccine for Children (VFC) program.[9] Increasingly, many departments of health and state professional boards are looking to make the CDC standards for proper vaccine storage and temperature monitoring of refrigerated and frozen vaccines their standard for proper storage and monitoring of all cold chain products.

The CDC lists three basic tenets for proper temperature monitoring and storage[10]:

1. A well trained staff.
2. Reliable storage and temperature monitoring equipment.
3. Accurate vaccine inventory management. This would also then include accurate inventory management for all cold chain products.

Proper Vaccine Storage Temperatures

Refrigerated vaccines should be stored at temperatures between 2°C and 8°C (36°F and 46°F). The thermostat should be set at mid range to achieve a temperature of about 5°C (40°F), which will decrease the likelihood of temperature excursions.

Vaccines stored in the freezer should maintain temperatures between -50°C and -15°C (-58°F and 5°F). The thermostat should be at the factory-set or mid-point temperature setting to assure appropriate frozen storage temperatures.

Proper Vaccine Temperature Monitoring

The CDC has always recommended that each unit storing vaccines must:

- Have a temperature monitoring device.
- Have temperature logs that are maintained and monitored daily for excursions.
- Log daily minimum and maximum temperatures.

The CDC has also refined the types of systems and solutions that should be utilized to be certain these recommendations are followed.

Part III: Solutions for Optimal Temperature Monitoring

Several years ago, maintaining manual temperature logs with manual thermometers felt adequate to meet temperature monitoring standards. This practice, however, allowed for potential temperature excursions that went unnoticed. Even when realized, these deviations could not provide the range of temperatures during the excursion, nor the duration.

Today's solutions are much more sophisticated, helping to ensure the temperature integrity of the product when dispensed or administered to the patient. For accurate temperature monitoring of refrigerated and frozen products, the system utilized should meet the following parameters.

1 The system should have a thermometer that provides continuous temperature monitoring with an active digital display. This provides the constant monitoring of temperature which assists in determining the stability of the refrigerator or freezer unit involved, and if it maintains acceptable temperature ranges throughout its cycle.

2 The thermometer should be certified and calibrated. In plain terms, this ensures the accuracy of the thermometer. The CDC recommends using only a calibrated thermometer with a Certificate of Traceability and Calibration Testing (also known as a Report of Calibration). This certificate, commonly known as a NIST certificate[11], provides the thermometer's level of accuracy compared to a recognized standard, and comes with the thermometer upon purchase. The CDC recommends that a current and valid Certificate of Calibration Testing (Report of Calibration) should include:

- Model / device name or number
- Serial number
- Date of calibration (report or issue date)
- Confirmation that the instrument passed testing (or instrument in tolerance)
- Recommended uncertainty of ± 0.5°C (± 1°F) or less

Many regulatory rules in a number of states point to the fact that they will only accept certificate validity for no more than two years prior to requiring recalibration or replacement.

3 Use of a digital data logger (DDL) is a must. Digital data loggers are electronic devices that may be programmed to record temperatures at intervals throughout the day. Currently the CDC recommends that the digital data logger be set to measure the temperature every 15 minutes.

4 The CDC recommends DDLs with the following characteristics:

A. Detachable probe in a thermal buffered material (e.g. glycol, glass beads, sand, Teflon) for all refrigerated and frozen products.

- Probes in a thermal buffered material provide a more accurate reading of actual product temperatures when placed in the same area where the product is stored. Fluid-filled products are more thermostable than air because they have a larger thermal mass. Standard probes that measure air temperature can fluctuate with the defrost cycles of the unit, frequent opening and closing of the door on busy work days, air circulation patterns, and more. This could lead someone to inaccurately interpret changes in air temperature to mean that the product temperature was out of range. Glycol-encased probes are the most commonly utilized thermal buffer material.
- Probes that directly measure air temperature are not recommended.

B. Alarm for out of range temperatures.

- Products requiring refrigeration should be stored at temperatures between 2°C and 8°C (36°F and 46°F).
- Products requiring storage in the freezer should maintain temperatures between -50°C and -15°C (-58°F and 5°F).
- Products requiring "controlled room temperature" should be maintained at a temperature that encompasses the usual and customary working environment of 20°C to 25°C (68°F to 77°F) and that allows for excursions between 15°C and 30°C (59°F and 86°F).
- The alarm for out of range temperatures is vital to determining if an issue is occurring. This allows for correction of the problem through thermostat adjustment or transference of the product to another unit or location.
- An alarm system can save products from becoming completely non-viable due to the excursion and/or preserve current product expiration dates.

C. Low battery indicator.

- The presence of a low battery indicator ensures that your temperature monitoring device will continue to be operational by alerting you to the need to change the battery prior to a power outage in the unit.

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D. Current, minimum, and maximum temperature indicator.

- Visually seeing the current temperature and the min/max range can allow for detection of a potential issue as it's occurring, which may then allow an adjustment to be made to prevent an excursion.

E. Recommended uncertainty of ± 0.5°C (± 1°F).

- To ensure temperature accuracy, it's necessary to maintain a temperature reference standard. This must include equipment and procedures that permit calibration of operating devices with temperature standards in a way that ensures minimum uncertainty, per the recommended NIST and CDC standard for these devices.

F. Logging interval (or reading rate) that can be programmed by the user.

- Being able to program this interval can be a vital component in meeting any regulatory monitoring and logging guidelines.
- During an excursion, especially one that occurs when there are no personnel present to hear an alarm (overnight, etc.), it's vital to know and

accurately log the interval and temperature range of the excursion. Having this data allows the provider to contact the manufacturer and receive accurate information regarding product viability.

5 A dashboard / software that allows both for the user to provide detailed documentation for each unit, and for the user to document actions taken and solutions to excursion issues.

- This should allow for printable monthly temperature logs to meet state regulations, as well as allow the provider and regulator to view issues and document steps taken to ensure product integrity.
- While many products have downloadable software, there's always a data privacy concern that accompanies it. No one wants to download software into a system that could potentially lead to a breach and compromise the integrity of HIPAA data. Safety first: Have a dashboard system available that's been vetted for security purposes and has a single secure sign-on system in place.

6 In a provider practice with multiple locations or a pharmacy chain, it's also advisable that the system report excursion issues that haven't been documented and addressed to team leaders for a location.

- It's advisable that the temperature monitoring reporting have the ability to be tailored to the leadership structure of an organization, and be changeable if that structure is altered.
- A chain of command protocol should be established and workable to provide leadership with continuous monitoring during an illness or vacation of an individual on the reporting chain.
- All personnel, especially those ultimately responsible for maintaining and utilizing the system properly, should have access to the reporting through a mobile application.

7 To meet the needs of the technology available for any provider, the ideal system will have the capability to be utilized via an Ethernet system, via Wi-Fi, or through a cellular system.

Conclusion: You, Your Patients, and Continuous Monitoring

The current nature of pharmaceutical products is such that proper storage can directly link to the efficacy of the product, and to patient outcomes.

We'll continue to see changes in regulatory rules, laws, and inspections that focus on the storage of pharmaceutical products in the effort to always be improving upon safe practices and patient wellbeing.

To ensure the health, wellbeing, and safety of patients, it will be vital that temperature monitoring is in place to enable certainty of product viability throughout the product chain of delivery or administration to the patient. It's integral that all staff at all locations be trained in the proper management and storage of all pharmaceutical products.

The most efficacious, practical, and thorough method to ensure proper temperature monitoring is to insist that your system meets the solutions listed above for both refrigerated and frozen products, as well as for ambient temperature monitoring of products that require controlled room temperature storage. Beyond ensuring product efficacy and maximizing therapeutic outcomes for patients, this system can also be a cost-saving tool. When excursions are addressed quickly and efficiently, you can minimize both product loss and potential danger to patients, both of which can cost your business money.

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