THE IMPORTANCE OF TEMPERATURE MONITORING FOR MEDICATION SAFETY & EFFICACY

A WHITE PAPER

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Executive Summary

Recent scientific advancements have led to a burgeoning variety of pharmaceuticals and vaccines on the world market for the prevention and treatment of disease. Recombinant DNA technology, monoclonal antibody development, and vaccine development have all played a role, and many of the new pharmaceuticals are complex and costly. As a result, more attention is being paid to the storage and stability of drugs and vaccines, many of which must be stored at correct temperatures to maintain potency throughout the cold chain—from manufacturer to wholesaler to point of care. Despite the need to ensure potency of drugs and vaccines, surprisingly little data are available concerning compounds stored incorrectly. In addition, U.S. regulatory bodies do not currently require rigorous temperature monitoring and real-time adjustment, despite numerous cases reported in the media and medical journals where unknown temperatures or temperature excursions led to wastage and lack of potency. For vaccines, improper storage can even create the need to re-immunize a population that was given a potentially sub-potent compound. Some experts are calling for more rigorous regulations concerning temperature monitoring. Leaders in health systems should be aware of the need for more rigorous monitoring of temperature-sensitive drugs and should work with system stakeholders to put appropriate monitoring and action plans in place. This white paper reviews background information on storage temperatures for drugs, evidence surrounding breaks in cold chain maintenance, and information on the U.S. Pharmacopeia (USP) task force. The authors make the following recommendations:

Given the cost and risk involved when drugs are not stored consistently at appropriate temperatures, **regulatory bodies** and standard-setting organizations such as USP are correct to review current policies and consider increasing the requirements for rigor and timeliness.

U.S. Boards of Pharmacy (the regulatory bodies that are usually responsible for drug storage guidelines) should independently examine the need for continuous temperature monitoring and develop plans to implement such monitoring.

Health system leaders (Directors of Pharmacy, Chief Medical Officers, Chief Nursing Officers, etc.) should compare the available systems for continuous temperature monitoring and determine which is most appropriate for their facilities.

Given the increasing importance of appropriate storage of pharmaceuticals, **manufacturers** are encouraged to make available existing stability information about their products to pharmacies, wholesalers, and others who store such products commercially.

Introduction

The biologic revolution of the late 20th and early 21st centuries has produced a staggering number of drugs to treat a variety of diseases. Innovative medicines that were developed in the last half century have had dramatic impacts on health outcomes, including morbidity and mortality. For example, childhood cancer survival rates have increased roughly 30% since 1970[1]. Medications against HIV have drastically decreased mortality (by 85% since 1995) and have turned a disease that was almost a guaranteed death sentence into a manageable chronic condition[2]. Atherosclerotic heart disease, the number one killer of Americans, has also been impacted by pharmaceuticals, with a roughly 30% decline in mortality in the last quarter century[3]. Complex proteins have been developed to treat a wide variety of disorders (such as rheumatoid arthritis, Crohn's disease, and severe asthma) that previously had few effective treatments. Breakthroughs in virology have led to effective treatments for hepatitis C, a leading cause of liver damage and cancer. Vaccine development has also accelerated in the last 25 years, with vaccines now available to protect against shingles, human papilloma virus (linked to cervical and other cancers), and invasive pneumococcal disease.

As might be expected, the research and development needed to produce these innovative compounds is very costly. An estimated $50 billion dollars is spent per year on drug development in the U.S.[4]. These costs are necessarily reflected into the industry that uses these compounds, and thus new drugs and vaccines, while often effective, are also expensive to the end users and their insurance companies. The cost to consumers for medications has risen by an average of 45% over the last decade[5]. Vaccine costs have also risen dramatically. The accelerated rate of drug and vaccine development shows no signs of slowing down. It is estimated that over 3,000 medications are currently in some phase of development worldwide[6]. As the potential for "personalized medicine" (medicine targeted to the unique genetic characteristics of a single patient) becomes more tangible, this number will surely increase. It is commonly stated that it costs a drug company over $1 billion and 15 years to develop a successful pharmaceutical or vaccine, and for every 1,000 compounds that are initially developed, only 1 makes it to market[4]. These costs are borne not only by the companies, but by the end users as well.

Given this dramatic increase in costs, more attention than ever is being directed toward the appropriate storage and transit of drugs. Indeed, the 2013 Drug Supply Chain Security Act mandated the development of systems in the U.S. that allow creation of a permanent record of a medication's fate as it travels from the manufacturer to the end user[7]. This law—colloquially known as "track and trace"—is designed to allow state or federal authorities to follow the distribution path of a medication down to the lot level with a record of all entities that accepted, stored, or transferred that product. Although the primary purpose of the Act was to prevent counterfeit or illegitimate product from entering the U.S. drug supply chain and being dispensed to patients, experts have speculated that as more sophisticated systems are put in place, more information about medications will be included in the track-and-trace record. This information may include storage conditions for pharmaceuticals and vaccines to ensure potency and safety.

Chemical Stability and Controlled Temperature of Pharmaceuticals

During the drug development process, pharmaceutical companies must determine the appropriate environmental conditions for storage and transit of their products. For marketing and sales reasons, manufacturers prefer that products be stored in the least restrictive conditions possible. Chemical analysis, however, often finds that the active ingredient content is transformed into degraded components (oxidized, hydrolyzed, and others), some of which are possibly toxic, if storage conditions are not correct. The longer the duration of exposure to the out-of-range conditions, and the farther out of range the temperature, the larger the amount of degradation by-products[8]. Analyses have also found that temperature excursions can change formulation properties, such as coloration of components, dissolution rate modification, or separation of emulsions. Products sensitive to low temperature lose their therapeutic properties after they have been frozen and the active ingredient structures have changed irreversibly. Thus, some products, such as some creams or biologicals, are sensitive not only to the absolute temperature but also to the temperature change itself because they lose their properties after freeze–thaw or other significant temperature cycles. To determine optimum storage and transit conditions, pharmaceutical manufacturers conduct small-batch testing of their product under a number of changing environmental conditions. There are several aspects to consider when planning these studies[9], including:

1 **Number and Size of Batches.** Initial stability testing is often performed on small batches of product. Generally, a minimum of three initial batches are placed into the long-term stability program to ensure batch uniformity for establishing an expiration date and environmental storage conditions. As part of an ongoing stability program and good quality assurance procedures, pharmaceutical manufacturers perform regular (at least annual) stability testing.

2 **Accelerated Studies Performed**. Manufacturers typically use an accelerated process of environmental changes, including temperature, to establish a tentative expiration date. This not only saves money (reduced lab time, faster to market), but also hastens the determination of appropriate storage conditions before the product undergoes clinical testing. This is reasonable because the purpose of an accelerated test is to determine batch uniformity, not kinetic degradation. However, some concerns have been raised about using accelerated studies to determine drug stability at high temperatures. Some experts have argued that the degradation mechanisms of these complex chemicals may be different at different temperatures[10], and that long-term testing to determine "real world" consequences of temperature differences or excursions should be performed.

3 **Test Intervals.** Although not mandated by most regulatory bodies, it is recommended that stability testing be performed directly after manufacture, every 3 months for the first year, every 6 months for the second year, and annually thereafter. However, more frequent testing near the anticipated expiration date is likely to give better information about the actual stability of the finished product. Testing at least annually is considered the minimum for compliance with Good Manufacturing Practice (GMP).

4 **Storage Conditions.** Whether a product was stored under controlled conditions or not, those actual conditions (temperature and humidity) should be recorded in studies. Merely stating that a product was stored at room temperature is not sufficient for the purpose of determining stability. USP defines controlled room temperature as being between 15° and 30°. A product stored for stability at or near 15° may have quite a different stability profile at its expiration date compared with a product stored at or near 30°. Based on published information, it appears that 24°–25° is a reasonable reference for studies examining the effect of thermal exposure at room temperature. When conducting stability studies, manufacturers should (and often do) perform these studies in conditions similar to normal storage conditions or, preferably, under exaggerated conditions. This is especially true for products designed for worldwide use.

"Room temperature" might be significantly different in Calgary, Canada, in January compared to Mexico City, Mexico, in July.

"Room temperature" might be significantly different in Calgary, Canada, in January compared to Mexico City, Mexico, in July. Products vulnerable to degradation by light or moisture should be studied in exaggerated conditions as well. Even if packaging is intended to protect the product from detrimental environmental conditions, data from small-batch studies would be helpful for wholesalers, pharmacists, and others, if improper storage occurs.

5 **Test Methods. CFR section 211.166[a3] requires that test methods be reliable, meaningful, and specific.** CFR section 211.165[e] gives more guidance by stating that the accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented. Section 211.194[a2] further requires that all testing methods used shall be verified under actual conditions of use. Testing procedures must include a stability-indicating test that will distinguish the active ingredient from any degradation products and be able to provide a reliable estimate of the quantity of any degradant. Manufacturers—who may contract with analytical laboratories to perform stability studies, or who produce product under contract for other firms—are ultimately responsible for the quality of the product. They must maintain records of all analytical procedures used and keep appropriate documentation to ensure their validity on file. Likewise, repackagers who rely on stability studies performed by the manufacturer must have copies of all analytical data necessary to support the expiration dating period.

6 **Container-Closure Systems.** It would be logical to assume that environmental testing for stability occurs in the same enclosures (bottles, vials, etc.) that would be commercially available. The FDA does require stability testing to be performed in the same container-closure system as the one that will be used when the drug product is marketed. However, the court case U.S. v Kaybel Inc. determined that repackagers do not have to obtain regulatory approval for the repackaged form of the product or for testing of the product in a new packaging system[11]. Thus, the effect of temperature variables on drugs that have been repackaged is often uncertain. That being said, it is the policy of the FDA's Center for Drug Evaluation and Research to allow repacking into container-closure systems that can be demonstrated to be at least as protective as, or more protective than, the original system without performing new stability studies prior to marketing. For example, current policy allows firms to repackage solid dosage units from plastic containers into

glass containers because glass has been shown to be a superior moisture and gas barrier. This policy does not apply to liquid drugs because of pH alterations resulting from the alkaline nature of glass.

7 **Container Sizes to be Tested.** When the same product is marketed in more than one size (e.g., bottles containing different quantities of tablets, drugs premixed in 50 or 100 mL of intravenous fluid, etc.), smaller containers have a higher internal surface area to volume ratio than larger containers. Because of this, smaller marketed containers are more vulnerable to product degradation in terms of the container properties itself. For example, moisture penetration through a 4 oz. bottle of tablets has the potential to be more detrimental than moisture penetration through a larger bottle of tablets. For this reason, when studying stability of a product marketed in several sizes of similar containers, testing of the smallest container size is imperative to be in compliance with GMP.

8 **Preservatives and Other Inactive Ingredients.** Pharmaceuticals often contain extra substances other than the active chemical for a variety of reasons. Most of these substances are chemically inert excipients that have no effect on the stability of the products. Desiccant packets are sometimes added to bottles to absorb moisture. Some drugs contain preservatives to inhibit microbial growth, which is important for preserving the sterility of the drug. The preservative itself and other additives should also be monitored throughout their shelf life to ensure their effectiveness. Once a minimally effective amount of preservative is established, chemical testing for the preservative(s) may be performed. The preservative system should be monitored when stability testing is done to monitor other active ingredients.

In summary, numerous factors, especially those surrounding GMP, should be examined when pharmaceutical developers determine the thermostability of their products. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) provides some guidance in this area, but most manufacturers generally design and perform temperature stability studies with the aim of covering the full range of storage conditions likely to be used by their customers.

Standard Methods for Measuring STORAGE Temperatures for Pharmaceuticals

Storage and transportation temperatures are highly significant factors in maintaining product quality throughout the distribution network. The distribution chain is seldom simple, and storage systems can vary enormously from the manufacturer to the wholesaler to the end user. In its simplest form, this chain involves shipment directly from the manufacturer to the customer or end user. In reality, the chain is rarely this short. It is more common for the distribution chain to involve a number of storage and transit locations, including airports and docks, and a variety of methods of transport, including aircraft, ships, and trucks.

An increasing number of drug products and vaccines require controlled storage and transportation conditions between 2˚ and 8˚, or between 20˚ and 25˚. Some of these, including vaccines, insulin, and biotechnology-derived products, must be protected from freezing.

Recommendations for storage temperatures given on product labels and in product literature are made to ensure optimum quality of the products throughout their shelf life. An increasing number of drug products and vaccines require controlled storage and transportation conditions between 2˚ and 8˚, or between 20˚ and 25˚. Some of these, including vaccines, insulin, and biotechnology-derived products, must be protected from freezing. Even a brief period at sub-zero temperatures may irreversibly denature proteins and cause a loss of efficacy. Therefore, such medicinal products must be maintained within a narrow temperature range above the freezing point but below a maximum temperature, which varies from product to product, throughout the distribution chain.

USP Chapter 1118 lists a number of temperature monitoring technologies[12] including:

- **Alcohol or mercury thermometers:** The volume of a liquid fluctuates as a function of temperature.
- **Chemical devices:** A phase change or chemical reaction occurs as a function of temperature, causing a change in appearance (examples include liquid crystals, waxes, and lacquers).
- **Chemical sensors:** A reaction rate or diffusion process is used to deduce a temperature equivalent integrated over time rather than the temperature at a specific moment in time (e.g., a spike or critical threshold).
- **Infrared devices:** The device measures the infrared radiation from the article whose temperature is being determined; this radiation varies as a function of the object's temperature.
- **Resistance temperature detectors:** The electrical resistance of a material changes as a function of temperature. Precision and accuracy depend on the quality of the electronics used to measure the resistance.

The ways in which temperatures are measured by drug manufacturers, transporters, and wholesalers vary considerably. Methods run the gamut from simple mercury-based thermometers that are read visually to sophisticated continuous temperature monitoring systems. Given the consequences that improper temperature conditions can have on medication potency, there is surprisingly little guidance and few regulations to direct those who manufacture, transport, and store these valuable compounds.

Again, it is important to remember that USP does not mandate (or even currently recommend) any specific device or monitoring technology for assessing temperature during storage of pharmaceuticals. USP requires only that the device be validated for its intended use (i.e., a device marketed for use in storage and transport of pharmaceuticals must be tested for that purpose). Variables that should be assessed in a validation scheme include measurement accuracy and measurement responsiveness. USP recommends that accuracy be validated with a device that is obtained from or traceable to the National Institute of Standards and Technology (NIST). Measurement responsiveness is the (relative) amount of time it takes the device to register a temperature change, and if available, correct time measurements[13].

When guidelines from standard-setting organizations or regulators are not followed (either intentionally or accidentally), one may suspect that the medications involved were not stored properly. What published information exists about incidents when temperature excursions occurred and the cold chain was broken—and what consequences occurred in these examples?

- **Solid state devices:** The effect of temperature on either an integrated circuit (see Thermistor below) or a micromechanical or microelectrical system is measured. These devices can attain the highest precision available and also produce a digital output.

- **Thermistors:** The resistance of this semiconductor device varies with temperature. Thermistors are able to detect very small changes in temperature and are accurate over a broad range of temperatures.

- **Thermocouples:** The junction potential of two dissimilar metals fluctuates as a function of temperature. Many metal pairs may be used, with each pair providing a unique range, accuracy, and precision. Precision and accuracy depend on the quality of the electronics used to measure the voltage and the type of temperature reference used.

- **Thermo-mechanical devices:** The volume of a solid material changes as a function of temperature, e.g., a mechanical spring expands or contracts as a function of temperature, thus opening and closing an electrical circuit or moving a chart pen.

Maintaining the Cold Chain

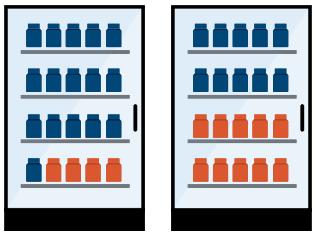
The term cold chain is primarily used with respect to vaccines, and refers to the maintenance of refrigerated temperatures for vaccines from the time they are manufactured through their shipment and delivery to health care facilities until their administration to patients[14]. Although many drugs and other biologic compounds require temperature-controlled storage, it is perhaps not surprising that vaccines have received by far the most attention and clinical studies regarding cold chain maintenance. Nearly all vaccines require temperature control during storage and transit, as they are inherently unstable products. The result of not storing vaccines appropriately may be substandard immunologic responses and lack of immunity, as well as the high cost of vaccine wastage and re-vaccination.

To ensure adequate transport and storage temperatures for vaccines, the Centers for Disease Control and Prevention (CDC) has provided the general recommendation of a narrow temperature range (between 2° and 8°, with a target of 5°) to maintain cold chain conditions[15]. In addition, each manufacturer provides storage guidelines specific to their vaccines on the package inserts. Factors determining the significance of a breakage in temperature maintenance include the presence of an adjuvant, whether the vaccine is live or inactivated, and whether the vaccine preparation is liquid or in lyophilized powder. For example, live attenuated vaccines are heat-sensitive, which can cause loss of potency at temperatures above the recommended range, but are stable at freezing temperatures. Other vaccines, such as those containing aluminum adjuvants, are freeze-sensitive. Exposure to freezing temperatures, even for a short period, may cause a loss of potency. Studies in animals have, to some extent, corroborated this notion.

One study with pertussis vaccines in mice found that freezing may contribute to low immune responses. In the murine model, researchers tested the immunogenicity of the antigens in the two forms of pertussis vaccine—acellular and whole cell. Some mice received vaccines stored in the ideal temperature range of 2° to 8°, while the other mice received vaccines stored below 0°. Immune responses were lower among the mice that received the incorrectly stored vaccines versus the mice that received the correctly stored vaccines[16].

Extrapolation of these data to humans is somewhat problematic. Human immune systems are complex and unique, and loss of activity of an improperly stored vaccine in mice or other animals may not translate to similar findings in humans. Several large human studies have been done concerning vaccine potency when the cold chain has been broken, primarily in developing countries—particularly those close to the equator where ambient temperatures can be well above 8°. Such countries may not have the resources or infrastructure to maintain cold chain conditions for vaccines, but often have populations that may benefit the most from immunization. The largest of these trials have been performed in Africa and Asia.

81% have refrigerators dedicated to vaccines



Only 50% have regulated temperatures

A 2015 survey from Cameroon found that 81% of health care facilities had a storage refrigerator dedicated to vaccines, but only 50% had temperatures regularly monitored[17].

A Tunisian pilot project that provided continuous temperature monitors in standard domestic refrigerators found that freezing of product was dramatically reduced from 13.8% to 1.7%[18]. This project also demonstrated that temperatures that are too cold can be as detrimental to vaccine stability as elevated temperatures[18]. In contrast, a study in Chad examined the stability of tetanus toxoid (vaccine) with a "controlled temperature chain" (up to 40° for less than 30 days before administration) in 2,200 women receiving the immunization. Tetanus antibody titers indicating immunity were found in over 95% of patients, suggesting that cold chain maintenance for this particular vaccine may not be necessary. Similar results were found in Benin with meningococcal A conjugate vaccine that was allowed to be stored up to 40° for up to 4 days. By the definition used in the Benin study, 15,000 vials of vaccine still needed to be discarded due to gaps in temperature monitoring[19]. Storage at room temperature did not affect antibody responses to hepatitis B vaccine in a 2006 study from Vietnam[20]. Resource-poor developing countries often have difficulty maintaining the cold chain; an example is a 2013 paper from Ethiopia that reported that only 19% of health care facilities had a refrigerator at all[21].

Older studies from other parts of the world suggest that accidental freezing of vaccines may pose a greater danger to potency than ambient temperature storage. One paper from 2004 found decreased potency of a hepatitis B vaccine that had been stored below 2 degrees[22]. A 2010 survey from Delhi, India found that low temperatures were more problematic in maintenance of the cold chain, with over 40% of medical refrigerators inspected below 2 degrees[23]. A systematic review from 2007 corroborated this information, suggesting that **up to 35% of vaccines worldwide are exposed to freezing temperatures[24].**

This seemingly common misconception that "colder is better" for vaccines demonstrates the need for education on this topic. However, data showing that such educational programs improve storage conditions for vaccines are limited. One paper from 2001 described a program from India in which 263 medical practices were divided into two groups; one group received education on proper vaccine storage and monitoring while the other did not. No significant differences in vaccine storage practices were found between the intervention and control offices. Only 26% of all the offices had written instructions for handling vaccines in preparation for immunization. Some clinics wrongly kept their refrigerator controls set lower because they thought colder temperatures were safer for vaccines, thus increasing the risk for freezing. Finally, only about 60% of clinics keep up-to-date temperature logs in the vaccine storage areas[25].

Although more recent studies have shown some improvement in proper vaccine storage and monitoring, there is significant room for improvement worldwide.

Although the biomedical literature is by no means replete with clinical studies looking at the outcomes of improper vaccine storage, numerous stories in the media have reported incidents where vaccines were wasted and discarded and patients needed to be revaccinated. A 2015 story about a large pediatric clinic in California described how an employee found freezing temperatures in a large vaccine refrigerator. Ten different vaccines, including those for whooping cough, polio, meningitis, rotavirus, human papillomavirus, and flu, had been stored in a malfunctioning refrigerator whose temperature had not been checked in several months. Given the potential for ineffective vaccines due to temperature

fluctuations, the office notified 1,551 families via letters and offered repeat vaccinations free of charge[26]. Another news story from California relayed a similar incident in which more than 4,000 patients were immunized with vaccines stored at freezing temperatures. Again, letters offering free revaccinations were sent to patients and their families[27]. A different incident of vaccines stored at freezing temperatures was responsible for about 2,000 Ohio patients needing revaccination against the H1N1 strain of the flu[28]. In 2008, more than 35,000 doses of influenza vaccine, which were frozen during transit, were administered before the error was found in a Kaiser Permanente hospital[29].

Not surprisingly, the process of vaccine wastage and revaccination is expensive. An Italian study estimated a cost to the Italian government of as much as 400,000 Euros due to improper storage of vaccines for diphtheria, tetanus, and pertussis (DTP), hepatitis B virus, poliomyelitis and Haemophilus influenzae type b[30].

A U.S. survey suggested that 1%–5% of vaccines are wasted, potentially costing up to **$31 million,** most of which can be avoided by fixing breaks in the cold chain[31].

Surprisingly, there are virtually no studies on lack of temperature control in the storage of pharmaceuticals besides vaccines. Two studies assessed loss of potency for insulin stored at higher than room temperatures and found only slight decreases in potency[32–33]. No information on the effects of freezing on medications was found in a Medline search.

Finally, it should be noted that all pharmaceuticals have some degree of thermal instability. Even medications designed to be stored at room temperature may lose potency, develop formulation degradation, or otherwise be rendered unsuitable for therapeutic use if proper storage conditions are not maintained. For example, in the event that a community pharmacy in Phoenix, Arizona loses air conditioning in July, drugs designed to be stored at room temperature may lose potency due to the dramatic increase in temperature. Although the focus of this white paper has been on storage of compounds that require refrigeration, there is a need for a consistent method of measuring environmental conditions, even for room temperature medications. It is notable that the authors' literature search could find no published papers on the consequences of improper storage of room temperature medications. Whether this is due to a lack of rigorous monitoring of temperature and other environmental conditions (such as humidity) or the absence of mandates by any standard-setting or regulatory body is unclear. This is an area that regulatory organizations and drug manufacturers, as well as end users, should explore in the future.

In summary, maintaining the cold chain for pharmaceutical products that need refrigeration is challenging, with research studies from many countries and media stories reporting frequent breaks in controlled temperature storage. Although the literature is somewhat inconsistent on the clinical outcomes resulting from improperly stored drugs and vaccines, it is clear that there is significant room for improvement in the monitoring of temperature throughout the transit and storage phase of pharmaceutical manufacture, and that education is needed about the consequences of vaccine freezing.

USP Standards for Drug Storage Conditions Including Temperature

As mentioned, USP has set forth standards related to the proper storage and distribution of medicines. An exploration of these regulations showed that many state pharmacy boards are following these guidelines for their own purposes.

Unless a medication label states a specific temperature range in which that medication should be stored, the medication is stored under the appropriate USP guidelines. Many medication labels state that the medication should be stored in a "cold" or "cool" place; however, these terms are subject to interpretation. USP defines "cold" as "any temperature not exceeding 8°"[34]. The temperature range should not fall below 2°. USP defines a "cool" temperature as "any temperature between 8° and 15°". For the purposes of this paper, "cold" is the term that will be focused on as it is the term used in reference to refrigerating a medication.

USP has provided basic guidelines for monitoring the temperature ranges listed above. Although not required, it is recommended that multiple devices are used to monitor temperature, and multiple locations where this information can be accessed should exist. Although manual systems for recording the temperature are accepted, it is recommended that automatic systems are used whenever possible along with an alarm system that indicates when the temperature falls below or exceeds the desired range[35]. USP does not mandate how often temperature is monitored, however twice a day for a manual system is the general practice observed by most pharmacy boards (Robert Lafaver, MS, email communication, 2/23/16). CDC recommends that systems using an automatic data logger should download the temperature recordings weekly[36].

Along with the guidelines set by USP, each state's board of pharmacy also has regulations in place regarding refrigeration of medications. A look at 20 states chosen at random (Table 1) revealed that the majority of pharmacy boards comply with the USP guidelines of a temperature range of 2° to 8°. State pharmacy boards that do not explicitly provide this temperature range as the guideline range typically require following the medication label's requirements for storing drugs, which are determined based on a manufacturer's standard operating procedures. Most states require that medications be stored in refrigerators intended for medical use only, with locked compartments. Nevada was the only state of those explored that explicitly stated that refrigerators are required to have an alarm system that alerts someone when the temperatures rise above or fall below the specified range[37]. Vermont was the only state of the 20 that said that if a manual system is being used, a "log compliance check at least monthly is required"[38].

Table 1. States Randomly Selected for Review of Temperature Monitoring Regulations

State	Temperature Range Guidelines	Recording Device Guidelines	Refrigeration Guidelines
Alaska	Follow USP guidelines	Manual or electronic	N/A
Arkansas	Follow USP guidelines	N/A	Locked compartment below food level
California	2-7C or manufacturers' recommendations	N/A	Manufacturers' recommendations
Connecticut	2-7C	N/A	Locked compartment for drug use only
Delaware	Follow USP guidelines	Appropriate recording devices should be used	N/A
Florida	Manufacturers' recommendations or official compendium	Manual or electronic	N/A
Georgia	Follow USP guidelines	Manual or electronic checked twice a day	Refrigeration for drug use only
Kansas	Follow USP guidelines or manufacturers' recommendations	N/A	N/A
Louisiana	2-7C	N/A	Refrigeration for drug use only
Maine	Follow USP guidelines	N/A	Refrigeration for drug use only
Michigan	Manufacturers' recommendations	N/A	Locked compartment in refrigerator
Nebraska	2-7C or manufacturers' recommendations	N/A	N/A
Nevada	Follow USP guidelines	N/A	Alarm system required
New Mexico	2-7C	Manual or electronic	N/A
North Carolina	2-7C	N/A	Refrigeration for drug use only
Pennsylvania	Follow USP guidelines	Manual or electronic	N/A
Texas	2-7C or manufacturers' recommendations	N/A	N/A
Virginia	2-7C	N/A	N/A
Vermont	2-7C	Electronically logged and checked each month	Refrigeration for drug use only
Wyoming	2-7C	N/A	Refrigeration for drug use only
N/A = Not available or listed			

Examples of Drugs with their Manufacturer Recommendations for Storage Temperature

Table 2. Acceptable Duration of Room Temperature Storage for Medications Labeled for Refrigeration

Drug Product	Brand Name (Manufacturer)	Acceptable Duration of Storage at Room Temperature	Source of Information
Basiliximab	Simulect (Novartis)	Contact manufacturer[a]	Manufacturer[b]
Cisatracurium	Nimbex (Hospira)	21 days	Package insert (39)
Daptomycin	Cubicin (Merck)	Contact manufacturer[a]	Manufacturer[c]
Digoxin immune fab	Digibind (GlaxoSmithKline)	30 days	Package insert (40)
Dornase alfa	Pulmozyme (Genentech)	24 hours	Package insert (41)
Eptifitabide	Integrilin (Merck)	2 months	Package insert (42)
Filgrastim	Neupogen (Amgen)	24 hours	Package insert (43)
Fosphenytoin	Cerebyx (Hospira)	48 hours	Package insert (44)
Infliximab	Remicade (Janssen)	6 months	Package insert (45)
Influenza virus vaccine	Fluzone (Sanofi)	Contact manufacturer[a]	Manufacturer[d]
Insulin aspart	Novolog (Novo-Nordisk)	28 days	Package insert (46)
Insulin detemir	Levemir (Novo-Nordisk)	42 days	Package insert (47)
Insulin glargine	Lantus (Sanofi)	28 days	Package insert (48)
Latanoprost	Xalatan (Pfizer)	6 weeks	Package insert (49)
Octreotide	Sandostatin (Novartis)	14 days	Package insert (50)
Pneumococcal polysaccharide vaccine	Pneumovax23 (Merck)	Contact manufacturer[a]	Manufacturer[c]
Ritonavir	Norvir (Abbott)	30 days	Package insert (51)
Rocuronium	Zemuron (Hospira)	60 days	Package insert (52)
Rotovirus vaccine	Rotarix (GlaxoSmithKline)	24 hours	Package insert (53)
Tobramycin inhalation	Tobi (Novartis)	28 days	Package insert (54)

a. Be prepared to give the following information: name of product, lot number, expiration date, maximum temperature stored, minimum temperature stored, and number of hours product was stored out of temperature range.

b. Novartis, oral communication, March 2016.

c. Merck, oral communication, March 2016.

d. Sanofi, oral communication, March 2016.

As seen in Table 2, there is much variation in the duration of time that a medication can remain stable at room temperature when it is labeled for refrigeration. A drug product's stability after a temperature excursion can range from hours to days to weeks and even to months. These data exemplify the importance of continually monitoring refrigerator temperatures to track temperature excursions. Although the package inserts for several refrigerated medications state the acceptable duration of storage at room temperature, there are many medications that require calling the manufacturer for stability results. Manufacturers typically do not share theoretical excursion data because their stability data are always changing and some data may be specific to a product lot number. Because temperature excursions do occur, and it may require significant time and resources to track down the correct response to the excursion (e.g., discard the drug, utilize within a shortened period of time, etc.), all parties involved in the distribution and storage of pharmaceuticals should have plans in place for managing this eventuality.

Conclusions

The lack of clear regulations concerning the correct storage of pharmaceuticals leads to avoidable loss of expensive product and can even necessitate revaccination of population groups. At the same time, the use of increasingly sophisticated pharmaceuticals will likely accelerate throughout the foreseeable future. In a humanistic and economic sense, drugs can be defined as extremely valuable cargo. Although guidance is available from regulatory bodies on the proper storage of drugs and the monitoring of drug storage conditions, the methods by which these functions are performed vary significantly. Even more importantly, practical information on the consequences of improper storage of drugs is scant at best. Given the critical importance of these compounds and the real world costs involved, it is suggested that the following action steps be considered by the appropriate organizations and stakeholders:

Regulatory bodies such as USP should review current procedures and regulations and increase the requirements for the rigor and timeliness of temperature monitoring and control.

In the U.S., the **state boards of pharmacy** (which are usually the regulatory bodies responsible for drug storage guidelines) should themselves independently examine the need for continuous temperature monitoring and consider developing plans to implement such monitoring.

Health system leaders (such as Directors of Pharmacy, Chief Medical Officers, and Chief Nursing Officers) should compare temperature monitoring systems that are commercially available and determine which systems are most appropriate for the needs of their facilities.

Given the increasing importance of appropriate environmental storage of pharmaceuticals, **drug manufacturers** should make available existing stability information about their products. In the future, manufacturers should incorporate systematic tracking and evaluation of storage conditions into their clinical trials and provide improved storage condition information to pharmacies, wholesalers, and others who store such products commercially.

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