Errors That Occur from Using an Inappropriate Thermal Buffer When Monitoring the Storage Conditions of Temperature Sensitive Products: Size and Material DO Matter

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Abstract
Common practice in the monitoring of cold chain conditions for temperature sensitive products is to employ a physical thermal buffer into which the temperature probe is inserted. This buffer may be a bottle of glycol or other liquid, a container of glass beads, aluminum block or nearly any other media the user feels appropriate. The purpose of the buffer is to simulate the experience of the stored product rather than the air temperature. Obviously, this mission will not be accomplished to the extent that the physical buffer is not matched to the thermal properties of the stored product and its container. Cold chain managers are faced with a complex problem if they attempt to take this issue into account. Furthermore, a match is not possible with a single physical buffer when the cold storage unit contains different products or size containers. This paper quantifies the results of this mismatch from various factors and suggests possible solutions to this dilemma.

Keywords: cold chain glycol storage, temperature buffer, temperature monitoring, vaccines

Overview

It is common in the cold chain monitoring of pharmaceuticals, vaccines, tissue and other temperature sensitive materials to require a temperature buffer consisting of a physical container into which the temperature probe is inserted. At the time of authoring this paper, there is no recommended or standard procedure for selecting this buffer. (Aldous, 2017) In fact, the specifics of the physical buffer--size, shape, and material--are very rarely consciously selected, but established by default to whatever the company providing the temperature probe uses. A review of physical thermal buffers currently provided by these companies shows little consistency in any of these parameters. Volumes can range from 10 to 300 ml glycol vials, as well as machined and preformed blocks of aluminum, plastic or silicone. The Centers for Disease Control and Prevention recommends a 20ml Boston Bottle filled with equal amount of water and glycol. The purpose of the water/glycol mixture is to prevent freezing of the buffering solution (CDC, January). However, the stored goods monitored by this buffer were observed to include pre-filled syringes as small as 0.25 ml to bottles and vials many times that volume.

The two purposes of the buffered temperature probe are somewhat in opposition to each other. A larger volume buffer will prevent "false" alerting from transient changes caused by regular use, however, that same buffer may to fail to respond quickly enough to freezing or warming events in time to prevent spoilage of the storage unit's contents. Both objectives can only be achieved when the buffer is thermally matched to the stored goods.

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Materials and Methods

When storing pharmaceuticals and other temperature sensitive products, each stored good must be stored according to the manufacturer's specifications. Most often the recommended temperature range is between 2° C and 8° C (36° F and 46° F) for refrigerators and between -50° C and -15° C (-58° F and +5° F) for freezers

Temperature excursions, short or long, cooling or warming, must be represented accurately to understand the effect on the stored contents. This is usually accomplished through periodic temperature reporting, with the intervals between readings varying from 5 to 30 minutes. While a short time excursion may not be damaging to the stored goods, the cumulative effects of repeated short events may degrade the contents. (GDP Question: When to use Mean Kinetic Temperature Calculation (MKT)?, 2014) This is especially true for the freezing of refrigerated goods where even a very brief freeze can destroy the stored goods. Consequently, it is of utmost importance to represent the temperature of the contents accurately when describing and recording the storage environment.

Glycol, beads, and sand are all used as a buffering material. All these loose media are subject to spill during normal access to the storage unit. This may have been the impetus for the development of the solid media buffers. These include

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temperature probes embedded in aluminum, Teflon™, or silicone forms. It is with these buffers that the thermal properties of the buffer are most influential.

Each buffer material has unique and varying physical properties. One such property is the Specific Heat Capacity (C_p) – Heat capacity or thermal capacity is a measurable physical quantity equal to the ratio of the heat added to (or removed from) an object to the resulting temperature change. (Resnick, 2013) For example, the specific heat of water is 4.18 J/g °C.

The terms that are used in the equation for calculating the specific heat of a substance are:

- Delta T or ΔT – *the difference between the first temperature T(1) and the second temperature T(2)*
- Mass m - *the mass of the sample*
- Heat Q – *the amount of heat in Joules J*
- Specific Heat C_p

The relationship between heat Q and temperature change ΔT is usually expressed in the form shown below.

$$Q = C_p \, \mathrm{m} \, \Delta \, \mathrm{T}$$

Equation 1 – Heat Transfer Rate Formula

This formula describes what is known as the Lump Capacitance Model (LCM). Not all materials are accurately characterized by the LCM. To determine if our buffer material is one of them we compute what is known as the Biot number.
The Biot number (Bi) is computed as:

$$Bi = \frac{L_c \, h}{C_p}$$

Equation 2 – Biot Number Formula

where:

- L_c - the ratio of the Volume to the Surface area V/A_s
- h – the conductive heat transfer of the storage unit, air = 100 w/m^2 K
- C_p – the heat capacity of the buffer material (see table 1) J/kg K

Biot values less than 0.1 imply that the heat conduction inside the thermal body is much faster than the heat convection away from the surface. This situation allows the use of the lumped capacitance model.

Material	*Bi*
Aluminum	0.00132
Ethylene Glycol, 50%	0.00036
Glass Beads	0.00141
Sand	0.00129
Silicon, RTV	0.00099
Teflon®	0.00094
Water	0.00028

Table 1 – Computed Biot Number (*Bi*) for Select Buffer Materials

The values in Table 1 were computed assuming a cylindrically shaped container. Since all the Biot values are considerably less than 0.1 we can rely upon the Lump Capacitance Model to describe the thermal reactivity of these materials.

The calculation of Specific Heat Capacity for our sample of buffer materials is shown in Table 2 below. We have included the density of each material as well to account for the differences in size of buffers.

	C_p Specific Heat	*p* Density
Material	**J/kg K**	**w/m^3**
Aluminum	897	2700
Ethylene Glycol, 50%	3270	1110
Glass Beads	840	1500
Sand	920	2660
Silicon, RTV	1200	120
Teflon®	1260	2200
Water	4180	1000

Table 2 - Specific Heat and Density of Buffer Materials (Specific Heat of Solids, n.d.)

Glass beads pose an additional challenge. Unlike a fluid or fine sand, the spherical shape of the beads does not fill the entire volume with the buffer material. This problem is addressed by answering an age-old carnival question "how many candies are in the jar?" Researchers at New York University (N.Y.U.) (Peeples, 2009) may finally have the answer to this classic mathematical puzzle. Their analysis determines that the randomly packed identical spheres fill up about 64 percent of the volume in each container. When sizing a glass bead buffer, this must be considered.

Given a standard of glycol volume and its equivalents, implementation of volumes greater or lesser would present a mismatch with the intended thermal response. The larger the buffer, the slower the temperature monitor will respond to the changes in temperature. Likewise, a buffer that is too small will fail to dampen the storage unit fluctuations which will result in false alerts during regular use and operation.

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For example the, CDC guidance for monitoring vaccines specifies the requirement for a thermal buffer but does not state how large or small it should be or what it should be made from. It does note, however; the purpose is defined below.

> "…a buffered temperature probe, which is the most accurate way to measure actual vaccine temperatures. Temperatures measured by a buffered probe match vaccine temperature more closely than those measured by standard thermometers, which tend instead to reflect air temperature."

As shown above in equation 1, to represent the *actual vaccine temperature,* it is necessary to consider the material and size or mass of the volume of the buffer.

Figures 1 and 2 below demonstrates the effect of the material and volume of the buffer. The data was developed using the following conditions. A stored material, e.g. vaccine is maintained at 4°C, the storage unit is subjected to an inrush of air that results in an air temperature increase to 12°C. Using the selected buffers and volumes, how many minutes would it take for the stored good to reach a critical temperature of 8°C?

The circumstances described herein are of a monitoring solution that is designed to alert when the represented contents exceed the upper control limit of 8°C. In this example, the stored contents are vaccines which are made up of mostly water. For the purposes of this demonstration, the stored good is in a 20ml cylindrical container. From the graph, it can be determined that the contents would reach the 8°C limit in approximately five (5) minutes. Further, the same material (water) using a 50ml buffer would not alert until 12 minutes. In this case, an improperly sized buffer would result in a delay of more than seven (7) minutes. It can be seen from the demonstration one can determine how the buffer size and material affect the time to alert.

Figure 1a and Figure 1b below demonstrates the effect of the selection of common buffer materials. In this presentation, the volume of the buffer remains constant, while the material is changed. In each case, a 20 ml volume of material is chosen. Except for glycol, the results indicate that none of the chosen buffer materials accurately represent the stored goods. To accurately represent the stored good, one must increase the size of each of the other buffers to match the characteristics of the stored good.

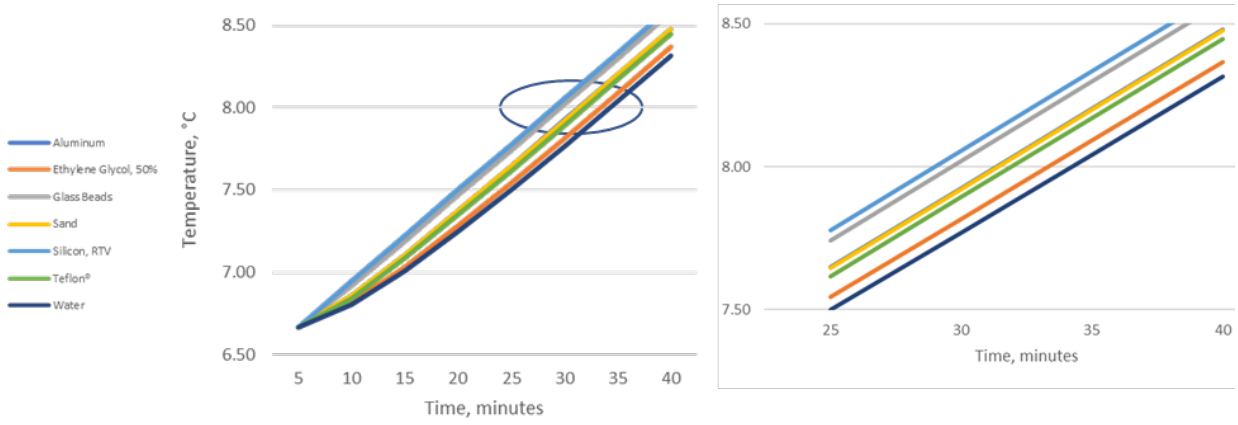

Figure 1a and 1b – Time to Temperature in Minutes for Various Buffer Material

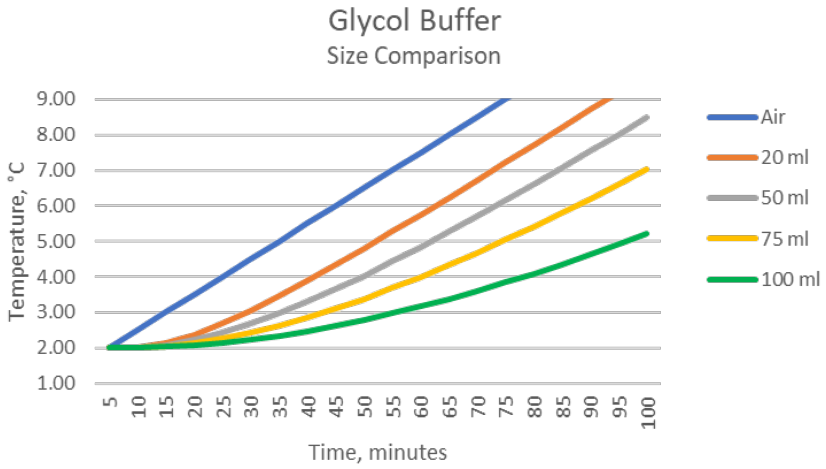

Figure 2 –Buffer Size Response Comparison (Warming)

Figure 2 demonstrates the result of applying different volumes of glycol buffers to the same warming data. In this case, the warming of the refrigerator is shown (fault condition – door ajar). The difference between a 20ml and 50ml buffer reaching the 8.0-degree level is 15 minutes. For a 100ml buffer this difference is 60 minutes.

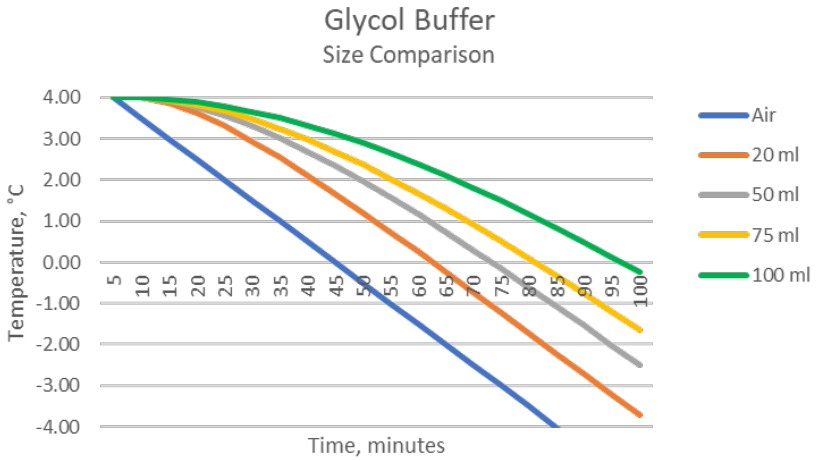

Figure 3 –Buffer Size Response Comparison (Freezing)

Figure 3 demonstrates the result of applying different volumes of glycol buffers to a cooling situation. (fault condition – stuck thermostat). When comparing the temperature of the air to the other buffer volumes, we can see the difference in the time it takes each buffer to reach freezing. Since the temperature probe is inserted in this buffer the storage manager would be aware of a freezing condition in widely different time frames.

Virtual Buffering

One solution to the problems identified above is a concept called "virtual buffering". This method involves a mathematical calculation to COMPUTE the temperature inside a container of known material based upon the thermodynamic equations and the temperature of the surrounding air.

The calculations involved with this method are not complicated, and are shown below:

$$\frac{dQ}{dt} = C_p\, A\, \frac{d}{dt}\,(\Delta T)$$

C_p = thermal conductivity constant
A = describes the stored container geometry
$d\Delta T/dt$ = Temperature gradient
dQ/dt is proportional to $T_0 - T_{ambient}$ and C_p A are constants

$y(t) = T(t) - T\infty$ Temperature difference between stored medium and air temperature

$y(0) = T(0) - T\infty = To - T\infty$ Initial temperature difference at t=0

$$\frac{dy}{dt} = \frac{d}{dt}\,(T(t) - T_\infty) = \frac{dT}{dt} - \frac{dT\infty}{dt} = \frac{dT}{dt} = -k(T_o - T_\infty) = -ky(t)$$

$$\frac{dy}{dt} = -ky(t)$$

$$\frac{\frac{dy(t)}{dt}}{y(t)} = -k$$

$$\int \frac{\frac{dy(t)}{dt}}{y(t)}\, dt = \int -k\, dt$$

$$\ln(y(t) = -kt + c = c - kt$$

$$y(t) = e^{C-kt}$$
$$y(t) = ce^{-kt}$$

$$c = (T_o - T_\infty)$$

$$T(t) - T_\infty = (T_o - T_\infty)e^{-kt}$$

$$T(t) = T_\infty + (T_o - T_\infty)e^{-kt}$$

Equation 3 – Algorithmic Buffer Equation

From Equation 3 above, an algorithmic model can be used to predict the thermal response of any shape, volume and material while using only air temperature. It should be noted, using the above method in bodies of simple geometry, e.g. cylinders, spheres, the error introduced by the assumption of uniform body temperature will be less than 5%. (Bergman, 2017) This formula was tested by comparing the theoretical data using Equation 3 and physical glycol buffering of the same size. The result was as the model predicted, the error was observed to be +5% / -3%. Demonstrated in an independent study, the accurate derivation of the constant *k* results in a much more accurate representation of the temperature of the stored contents with an error of .5%. (Rusnack, 2018) . With the ability to represent the temperature of the stored goods, while providing an equivalency of buffering the air temperature, it is no longer necessary to utilize a physical buffer. The recorded raw air temperature can be acted upon providing data that would be otherwise masked by a buffered temperature.

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Conclusion

This paper has attempted to quantify an intuitively obvious fact: that thermal buffers of different size and composition will react differently to changes in ambient temperature. The actual consequences of this discrepancy will depend upon the sensitivity of the store goods. With the increasing presence of biological drugs and their synthetic version "biosimilars" this would seem to be an increasingly important issue.

Selection of the thermal buffer that is used in the monitoring of temperature sensitive materials should not be simply left to the provider of the monitor system. It should be accomplished with great care and understanding of the desired outcome. The following should be considered in the selection process:

- What are the physical properties of the materials being stored?
- What is the range of package sizes being stored?
- What is the buffer material selected as the buffer?

Knowing these three factors, one can properly size the buffer that will accurately represent the temperature of the stored goods while providing true and timely notification in the event of a temperature excursion.

In those situations where the stored goods are encased in a variety of enclosures, or when they may vary from time to time, it is obviously impossible to accomplish this completely. The option of "virtual temperature buffering "could be the best solution to these situations.

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