PERSPECTIVE

A Case for Expanding Thermochromic Vial Monitor Technology to Insulin and Other Biologics

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Insulin quality and efficacy determine glycemic control, which determines quality of life for people with diabetes. Insulin efficacy is reduced by heat exposure, especially in tropical climates, remote areas, and with improper handling. Insulin doses can be adjusted based on blood glucose monitoring, which may compensate for lack of viability. However, a measured response may be difficult with other biopharmaceuticals. Thermochromic vial monitor technology developed for oral polio vaccines (vaccine vial monitors) is an inexpensive, easily available, visible modality which can be used for insulin and other biopharmaceuticals to detect excessive heat exposure and thus reduced potency at any point in the cold-chain, till the end-users, thus improving patient care. Regulatory authorities must urgently consider the need to impose mandatory use of this technology for all biopharmaceuticals, including insulin, to ensure efficacy till end usage.

Keywords: *Drug stability, Drug storage, Efficacy, Temperature*.

Glycemic control determines quality of life (QoL) and the risk of acute and chronic complications in diabetes. Insulin quality is a major determinant of glycemic control, especially in type 1 diabetes. The efficacy of a biological product like insulin depends on its temperature during manufacture, transport, and storage till end-use. Exposure to high temperatures at any point reduces potency, resulting in blood glucose fluctuations, impeding diabetes care and thus QoL.

The effect of high temperatures on insulin has long been realized to be a problem in tropical countries. Vimalavathini, *et al.* [1] studied the effect of temperature on regular and biphasic insulin made by three manufacturers both *in vitro* and *in vivo*. They reported that storage at 32 ºC and 37 ºC decreased potency by 14%-18% by day 28. Carter, *et al*. [2] reported that the average intact insulin concentrations were only ~40 U/mL in regular and NPH 100 U/mL insulin vials, made by a US and a European manufacturer, and bought from retail pharmacies. They speculated that since manufacturing processes are tightly controlled, vagaries in the cold chain impacted insulin concentrations [2]. This study was criticized by pharmaceutical employees [3,4] for serious methodology flaws and by the American Diabetes Association (ADA) [5] for small sample size and methodology issues. The criticism; howsoever justifiable, does not take away from the issue that we can never be sure of insulin viability.

Blood glucose levels are affected by many factors, making day-to-day control difficult. Patients are educated to make extremely complex adjustments by frequent glucose testing, anticipating the effect of food and exercise and compensating for fluctuations. Technology, including continuous glucose monitoring systems (CGMS) and insulin pumps, has helped tremendously, but is expensive. However, a factor as important as insulin viability has not received enough attention. Patients can never be completely sure about potency and viability of insulin in any vial, and whether insulin storage at their end is optimum during usage. The ADA, and American and European regulatory authorities may be able to ensure that in wealthy, mostly non-tropical settings, insulin would get effective cold chain storage till usage, and feedback from CGMS would compensate when viability is reduced. However, the situation may differ, with gaps in cold chains, in tropical countries where summer temperatures can soar up to 48 ºC.

What happens after the insulin is purchased? In an observational study in summer 2015 from India, Patil, *et al*. [6] found that over 25% patients were keeping insulin vials outside the recommended temperature conditions (at room temperature or in the deep freezer) and 98% were transporting insulin during travel without maintaining the cold chain. Our experience in a pediatric diabetes clinic, with regular diabetes education and reinforcement, was similar. Between May and August 2014 (maximum temperatures 36-41 ºC), 9% patients had used no cooling

method during transport and insulin temperature ranged from 4-33 ºC, exceeding 25 ºC in 26% cases. If this was the situation with adequate patient diabetes education, the vast majority of insulin users would be considerably worse off with the resultant poor glycemic control leading to chronic and acute complications, including ketoacidosis.

Thus, knowing that, insulin loses potency on heat exposure, it is used by non-professionals with varying degrees of education and intelligence, that the majority of patients do not have access to sophisticated technology to monitor for the vagaries of insulin viability, and that the impact is clinically significant, the importance of maintaining insulin at the correct temperature till the end of usage, and the associated difficulties are incontrovertible. This is also true of all other biopharmaceuticals like teriparatide or growth hormone, which are equally vulnerable to heat, but have no mechanism like CGMS to help compensate if potency is redued. As the range of biopharmaceuticals expands, there is a greater need for ensuring these molecules are maintained in strict temperature conditions throughout their supply chain, till end-usage.

POLIO VACCINE AND COLD CHAIN

In 1988, the global initiative to eradicate polio was launched. The challenge of ensuring the oral polio vaccine reached every baby in every household, village and city across the world, with retained efficacy, was a critical concern as the vaccine is extremely vulnerable to high temperature, routinely seen in tropical and subtropical countries [7]. The response to the appeal by the World health organization (WHO) [8] and PATH [9] for an accurate, easy-to-use and cost-effective method to monitor the heat exposure of the vaccine, resulted in the development of the vaccine vial monitor (VVM) technology. The VVM is a small thermochromic label which adheres to the side of the vial. It is composed of chemicals that irreversibly change color on exposure to heat, with the rate of change dependent on the temperature and the length of time exposed. VVM technology has played a major role in eradicating polio from the world and is talked about as one of the great successes of science. It identified the vaccine vials overexposed to heat, so they could be discarded, ensuring safe and efficacious vaccination coverage, and also identified which had been exposed to heat but were still usable, preventing vaccine wastage [10,11]. This technology costs little and is already widely available and used. The limitations of VVM technology have been well-studied and discussed. Srivastava, *et al*. [12] pointed out that VVMs record only increases in temperature and not decreases; they do not respond perfectly to rapid fluctuations in temperature; and cannot provide information of all the temperature fluctuations experieced. However, these limitations do not impact the chief purpose of these thermochromic vial monitors, *i.e.* allow the end-user to simply, and directly evaluate whether to use a particular vial or not.

NEED FOR UNIVERSAL IMPLEMENTATION

Thermochromic vial monitor technology has not been widely adopted by the pharmaceutical industry in spite of the low cost, easy availability, and eminent desirability. If this technology is used, end point users like patients and health workers can discern the potency of the drug in any vial. When supply chains are properly maintained, the thermochromic monitor would serve as an indicator for optimum insulin storage. If insulin is not being stored or transported with adequate care, the breakdowns during handling can be identified, and improvements made. The utilization of more sophisticated technology such as electronic monitors and digital data loggers to track the minute-to-minute fluctuations in temperature in sealed consignments [13,14], while necessary for ensuring proper transportation of biopharmaceuticals, are not sufficient as their access and reach are limited. The simple visible thermochromic indicator would afford the patient a greater degree of control over purchase and discard, offsetting the cost increase of each vial with the societal benefits it confers, such as better medical outcomes. Perhaps it is optimistic to think that any single pharmaceutical company would initiate this process, which may increase prices and make its products uncompetitive. Therefore, the push can only happen when it comes from regulatory authorities, and applies to all the manufacturers.

The medical community needs to urgently wake up to this cost-effective, reliable, and configurable technology, and put pressure on regulatory authorities to demand universal application for all biological drugs. So far, this has not happened in the developed world. Perhaps it is time for governments in developing, tropical countries like India to take the lead in the matter, rather than waiting for the push to come from elsewhere. This would improve medical care not only for diabetes, but for several disorders; not only in the tropics, but across the globe.

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