Insulin Storage Guidance for Patients with Diabetes Using Insulin

In the year 2020, insulin products worth over INR 3000 crores were sold in India. Over 75% of this insulin was marketed by multinational companies and the remaining one-fourth by Indian companies. However, most of the insulin regardless of who marketed them was manufactured in India. Only a small percentage of newer analogs are currently imported into India.[1]

At any given time in our country, many millions of these insulin vials, prefilled pens, and cartridges are either in transport maintaining the cold chain, in storage in temperature-controlled warehouses, or in monitored and unmonitored pharmacy refrigerators around the country, or placed in unmonitored domestic refrigerators at homes, offices, schools, hospital wards, and clinics, packed into pockets, purses, bags, backpacks, briefcases of patients with diabetes (PwD), stashed in glove compartments of cars and in overhead bins of aircraft and at many times left on dining tables, bedside tables, sideboards, cupboards, kitchens, bathrooms and assorted places in the homes of PwD.

All insulins including analogs insulins are prone to physical and chemical degradation over time which then leads to a corresponding loss of potency. Fluctuations in temperature, exposure to direct sunlight, shearing stress when insulin containers are agitated, and exposure to air with an increased air-liquid surface which happens when there is a decrease in volume because of usage in a vial and inadvertent freezing followed by thawing are the major factors that lead to insulin degradation. The two major chemical pathways for insulin degradation include deamidation and polymerization. Both the deamidated and polymerized insulin metabolites still retain some glucose-lowering potency. In contrast, the primary physical pathway for degradation is the slow aggregation of insulin molecules into fibrils. Stable bonds between insulin molecules within the fibrils prevent their absorption when they are administered subcutaneously. Physical degradation can be confirmed under microscopy but can also be detected by visual inspection of the vial. This is may be more difficult to visualize in newer cartridges and prefilled pens.[2]

The stability of an insulin preparation would be measured by measuring the persisting potency of the preparation over its travel from the manufacturing site to the home of the PwD. In the past potency of insulin were measured using biological assays in rabbit and mice to document glucose-lowering capacity. One unit of insulin historically was the amount of insulin required to produce hypoglycemia (seizures) in an adult rabbit. Today most pharmacopeias recognize high-pressure liquid chromatography (HPLC) as the standard method to assess insulin potency.[3] All insulin manufacturing companies in India have invested in good manufacturing practices to improve the stability of insulin produced at factories and in resources for temperature-controlled transport and storage all along the supply chain till the insulin reaches the pharmacy. Once insulin reaches the pharmacy or the hospital it is supposed to be stored in a temperature-controlled and monitored pharmaceutical refrigerators. A daily documentation of minimum and maximum temperatures is recommended but rarely followed. Supply chain guidelines that are followed and the quality assurance tools for insulin are summarized in Figure 1.[4]

At the end of the supply, chain insulin finds its way to the homes of patients with diabetes or to hospital wards. The limited guidance at this point includes package inserts which in most cases mention that insulin formulations should be stored in a refrigerator between 2-8 degrees and discarded once it is beyond the documented date of expiry. Alternatively, the package inserts mention that insulin can also be stored at room temperatures (15 -30 degrees) provided it is used within a certain time which could range from 14 days (Isophane insulin) to 8 weeks (Insulin Degludec). For most insulin formulations, unused insulin kept at room temperature should be discarded after 28 days.

Guidelines on Insulin Storage at Homes of Patients with Diabetes

In this issue of the Journal Pande *et al.*[5] publish a survey of physicians' attitudes to alternative strategies for insulin storage in the absence of electricity or refrigeration. The survey was undertaken during a regional diabetes conference and 188 physicians (of whom 93% prescribed insulin) responded to the questionnaire. In absence of refrigeration use of clay pots, icepacks, and thermos flasks were suggested for use at home. For travel purposes, in summer, the use of clay pots, thermos flasks, icepacks, etc., was suggested.[4] However, what was clear from the survey was the lack of clear guidelines for insulin storage at home despite the large number of patients using insulin in our country. A multinational, multicentric study from Africa and South Asia suggested that evaporative devices like clay pots and goat skins could be used in resource-poor countries to keep insulin cool and were effective.[6] However, a recent guideline from the East African Diabetes Study Group discouraged the use of clay pots because of hygiene and contamination issues.[7]

Guidelines are sparse but the available ones are summarized in Table 1.[7-10]

What remains common in all the guidelines is the adherence to the manufacturers' instructions that unused insulin should be

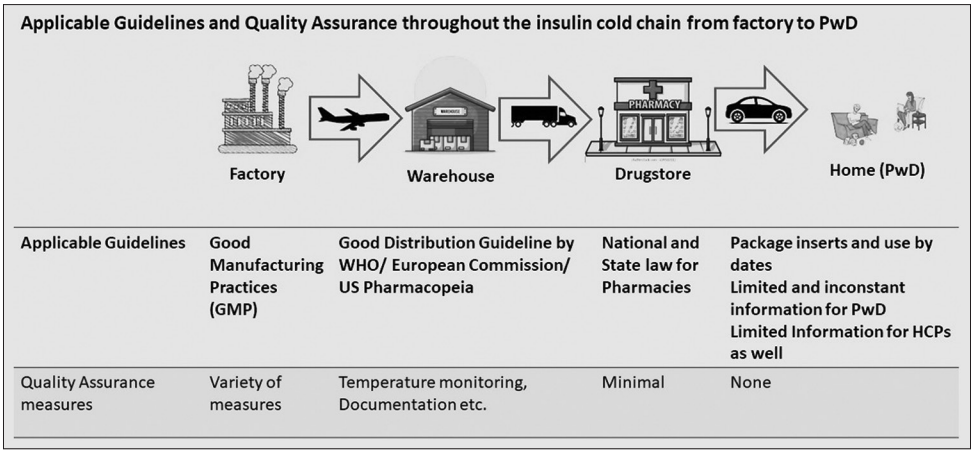

Figure 1: The supply chain from manufacturer to end-user (the person with diabetes) has robust quality assurances (QA) and guidance along the first part of the chain but has sparse guidelines and QA in the second half of the supply chain of insulin. [*Abbreviations- WHO- World Health Organization, PwD- Person with Diabetes, HCP- Health Care Professional*]

Table 1: Published insulin storage guidance –Similarities and differences

FITTER India Guidelines[8]	IDF Europe[9]	ISPAD Guidelines[10]	EADSG Guidelines[7]
"Specific storage conditions provided by the manufacturer should be followed. Insulin should be stored in a cool (below 30°C), dark place and must be protected from extremes of temperature such as direct sunlight, kitchen, closed cars, green houses, top of the refrigerator, and television (A3). Insulin pens and vials, which are not in active use, should be refrigerated, but not frozen (A1). Pens should never be stored with needles. In places where a refrigerator is not available, it is advisable to put the vial in a plastic bag, tie a rubber band, and keep it in a wide mouthed bottle or earthen pitcher filled with water."	"General recommendations on how to store insulin (vials and cartridges) • Carefully read the insulin's package leaflet since it might include specific information for that specific product. • Vials and cartridges of insulin not currently being used should be stored in the refrigerator (2-8°C) until their expiry date. Do not use insulin. • If the expiry date on the vial or cartridge or prefilled pen has been reached. • If the clear soluble insulin has turned cloudy. • If the insulin is discolored. • If the insulin has been frozen or exposed to high temperatures. • If the insulin contains lumps or flakes or sticks to the glass. A few simple measures can effectively reduce the risk of freezing: • Using an airtight container to store medications inside household refrigerators to reduce temperature fluctuations. • Keeping a thermometer to measure (and ideally log) temperature directly next to the medications. • When using cool bags with ice or ice packs to transport insulin, making sure pens and vials are not in direct contact with the ice packs."	"The individual manufacturer's storage recommendation and expiry dates must be adhered to. • These usually recommend that: • Insulin must never be frozen. • Direct sunlight or warming (in hot climates or inside a car on a sunny day) damages insulin. • Patients should not use insulin that has changed in appearance (clumping, frosting, precipitation, or discoloration). • Unused insulin should be stored in a refrigerator (4°C-8°C). • After first usage, an insulin vial should be discarded after 3 months if kept at 2°C to 8°C or 4 weeks if kept at room temperature. However, for some insulin preparations, manufacturers recommend only 10 to 14 days of use in room temperature. • In hot climates were refrigeration is not available, cooling jars, earthenware pitcher or a cool wet cloth around the insulin will help to preserve insulin activity."	"Ideally, insulin should be stored in a refrigerator between 2 and 8 C and should be protected from light when vials or pens are unopened. Most families in East Africa do not have refrigeration facilities in their homes, and therefore, other methods of safely storing insulin should be devised. Vials in use may be kept at room temperature (20–25 C), protected from sunlight, for 6 weeks, and 4 weeks if the temperature goes up to 30 C, in a clean plastic box. Storage at a higher temperature during use may degrade the insulin or convert it to higher molecular weight components. Patients with diabetes need to be educated about temperature variations and duration of storage of insulin vials for maintaining the efficacy of insulin. Keeping insulin in clay pots is likely to cause contamination as it is difficult to keep it clean: this should be avoided. • Clay pots have been previously recommended."

stored in a refrigerator between 2-8 degrees. Most PwDs even in developed countries have household refrigerators at home. These are primarily designed to store food not drugs and are optimized for food safety (0-4 degrees). This is a few degrees below what manufacturers recommend and at the lower end reaches the freezing point. Additionally, unlike pharmaceutical refrigerators, household refrigerators do not have air ventilators to circulate the temperature evenly. This would mean that

within the refrigerator there could be areas that approach freezing temperatures even within the regular compartment of the refrigerator. Household refrigerators also show significant day-to-day and hour-to-hour variations in the temperatures maintained inside. In a recent study, Bluetooth-enabled temperature sensors was placed next to insulin stored in household refrigerators by 338 PwDs. Deviations were found in all the sensors placed in the refrigerators with sensors being out of range 11.3% of the time. 17% percent of the sensors revealed excursions below freezing point.[11]

Suggestions from the International Diabetes Federation (IDF) Europe awareness paper for insulin storage include using an airtight container to store insulin within the refrigerator, avoiding small refrigerators including dorm-style and hotel mini-bar refrigerators which tend to freeze more than larger household refrigerators, and keeping a thermometer next to the insulin and regulating the thermostat based on the inputs.[7]

Way Forward

What the current paper exposes is the lack of clarity among HCPs about how they should educate a PwD who is prescribed insulin regarding insulin storage. This is not surprising considering whatever limited guidelines that are available to HCPs are just reflections of the guidance printed by insulin manufacturers in package inserts accompanying the product. The lack of guidelines is also probably a reflection of the fact that there have been limited studies and quality audits on the last and vital leg of the insulin cold chain (storage in the home of PwD) prior to its administration. Since most of our required insulin is manufactured within the country, insulin manufacturing companies should be encouraged to undertake work to improve the science and guidance about insulin storage at the homes of PwDs in all kinds of situations and climates.

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Quick Response Code:

Website: www.ijem.in

DOI: 10.4103/2230-8210.374161

How to cite this article: Jacob JJ. Insulin storage guidance for patients with diabetes using insulin. Indian J Endocr Metab 2023;27:93-5.