



## Preserving Efficacy of Temperature Sensitive Medicines–Logistics Management in Pharmaceutical Supply Chain

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### ABSTRACT

*Protecting the efficacy of temperature-sensitive drugs is a real challenge especially for the countries with hot climates. Over-the-counter medicines have recommended storage-temperature of around 20-30 °C, while ambient temperature in most metropolitan areas of Pakistan reach around 40-50 °C in summers, even under the shade. Other temperature-sensitive medicines require storage at around 4-8 °C. A reputation of spurious drugs due to mismanagement with regard to transport and storage also goes contrary to the interests of the pharmaceutical sector. This research investigates the preservation and storage of temperature-sensitive medicines in its specialized supply-chain (referred to as “cold chain”) and finds that while the import of active ingredients is rather well managed and controlled with storage at within the desired temperatures; the distribution-chain needs to be more adaptive of the standards in-order to better preserve efficacy of the medicines. Nevertheless, long hours of power black-outs (a common occurrence in Pakistan and other developing nations) further guarantee the deterioration of temperature-sensitive medicines stored at the chemist-shops. It is therefore, recommended that temperature-sensitive medicines should only be dispensed from stores that have standby-power.*

**Keywords:** Pharmaceutical industry, cold supply chain, temperature sensitive medicines, imported medicines.

### Introduction

#### Overview

Appearance of polio virus among the children who have received several doses of the polio-vaccine is clear evidence that the efficacy of the medicine is being compromised. Polio

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vaccine requires storage temperatures of 2-8 °C, whereby very cold temperature is also undesirable and in the case the vaccine becomes frozen it needs to be discarded.

Pakistan has a hot climate where temperatures in the shade often exceed 40 °C. If left unprotected, temperature inside a van or truck could even exceed 50 °C during transportation. Most normal pharmaceutical products require storage at ambient temperatures of about 20°C, while others require even lower temperatures of about 4 °C, and still some require even lower storage temperatures (Bishra, 2006). Maintaining a cool supply-chain from production till the time of administering the medicines are therefore, important in maintaining the efficacy of pharmaceutical products.

Logistics of pharmaceutical distribution and assurance that the medicines are kept at temperatures required for their storage is a challenge of significant proportion in Pakistan. Pharmaceutical companies have the responsibility of ensuring that transportation of medicines is carried out in vehicles that can maintain required temperatures. In addition, the storage of pharmaceutical products at distributors and chemists also needs the required refrigeration (Bishra, 2006). Contrary to the requirements, the highly sensitive and expensive medicines are often supplied through a limited number of reputable stores or through the sales representative of pharmaceutical companies.

The maintenance of cold supply chain is receiving considerable attention of major pharmaceutical companies but downstream supply chain requires much more attention in order to ensure that the product reaches the patient without any damage due to problems in cool chain process.

This research investigated the various factors affecting the logistics of temperature-sensitive medical products, which includes shipment of medicines, finished product temperature-control and proper temperature control in the complete value chain of the medicines.

## **Literature Review**

Medicines require storage at temperatures at which they can retain their usefulness until their expiry date. Coleiro (2012) studied the medicines, which are normally available at large chemist shops and found that out of the 1794 medicines included in the study that are recommended for room temperature storage; 1039 required storage below 25 °C, nearly 25% (414 medicines) recommended storage-temperature of 30 °C, and 334 did not mention any specific temperature. The room temperature of 25 °C might be considered normal for some of the European countries but in most other part of the world (including Pakistan) temperature under the shade often exceeds 40 °C. In yet some other countries, room temperature if not controlled can be near freezing-point. It is therefore, important to protect even normal “room temperature” requiring medicines from normal-ambient temperatures, which can come to be very hot and very cold depending on the season and climate.

During transportation, temperature inside a closed container can exceed 50 °C. Even ordinary above-the-counter medicines lose their efficacy at these kinds of extreme temperatures (Konrad, 2011).

## **Effect of Temperature on Sensitive Medicines**

In addition to normal medicines, vaccines, specialty medicines, and blood and its derivatives are much more sensitive to temperature; they require cold storage (Coleiro, 2012). Vaccines for Measles, Mumps, and Rubella (MMR) are considerably sensitive to temperature and sunlight (World Health Organization [WHO], 2009); a slight negligence in this matter ultimately damages the medicines. The World Health Organization’s assessment report (WHO, 2009) shows that out of 70 countries, only 29% of the countries follow minimum

requirements of temperature control in medicine storage and transport. Due to improper arrangement of cold-chain-logistics, shelf-life is shortened and in worst case scenarios, products are ruined. Biologics are most stable at around 2-8 °C. Vaccines, insulin, and blood pressure products have high storage-temperature associated risks; whereas, sub-zero temperatures may permanently denature proteins, leading to loss in efficacy. Bishra (2006) mentioned that more than \$400 billion of pharmaceuticals that were sold in 2003, nearly 10% were biopharmaceuticals; given that these are temperature-sensitive medicines, clearly shows that the cold chain makes up an important part of pharmaceutical supply chains. For vaccine transportation and storage, Madhukar, Kumar, and Khattri (2013) emphasized that temperature should be maintained between 0°C and + 8°C, since vaccines losses their potency when exposed to heat while their outward appearance remains unchanged. Risk of damage is increased where relative humidity (RH) level is comparatively high, such as in cold rooms and cold transport because of humidity the medications become softened and crumbled (Taylor, 2003).

Effect of temperature on medicine is further demonstrated by the research work from Bhadra, Gupta, Bhadra, Umamaheshwari, and Jain(2004), which showed the effect of temperature and multilayer capsule material on ciprofloxacin hydrochloride, an antibiotic that requires storage at 4- 10 °C (Table 2.1). When exposed to temperatures of 25- 10 °C and 50- 10 °C, the potency of medicine after storage-periods fell with the increased temperature exposure over longer durations.

**Table 1: Effect of temperature and duration of exposure on medicine potency (Bhadra, Gupta, Bhadra, Umamaheshwari, and Jain, 2004)**

Formulation code		No. of days of storage					
		LBL-1			LBL-2		
		10 days	20 days	30 days	10 days	20 days	30 days
% Intact capsules left on storage at	4±1°C	97.1±0.8	94.6±0.7	92.1±0.6	98.3±0.5	97.5±0.6	92.47±0.8
	25±1°C	94.8±0.9	89.3±0.5	85.46±0.7	92.4±0.5	86.4±0.4	83.42±0.6
	50±1°C	87.6±0.8	81.8±0.6	75±0.3	80.8±0.6	75.7±0.7	62±0.5
% Residual drug content left on storage at	4±1°C	95.8±0.4	93.1±0.6	91.7±0.8	94.9±0.6	91.7±0.9	89.8±0.5
	25±1°C	97.2±1.2	96.3±0.6	94.8±1.2	92.8±0.8	86.4±0.5	82.5±0.4
	50±1°C	80.5±2.5	75.6±1.8	62±1.5	75±0.3	68±0.8	55±0.5

LBL-1 refers to one kind of capsule and LNL-2 refers to a multilayer capsule.

### **Classification of Temperature for Storage & transportation**

Based on temperature requirements by Rankin, Quick, Laing, & O'Connor (1997) study, the storage requirements of medicines are classified as below:

#### **Store frozen**

Vaccines and insulin need to be transported at sub-zero degree temperatures, while sometimes can be stored at -20 °C.

### **Store at 2°C - 8°C**

This is normal temperature for the storage of any temperature-sensitive medicines, and must be kept in the middle part of the refrigerator.

### **Keep cool**

This term is used when a medicine must be kept at temperatures 8 °C- 15 °C.

### **Store at room temperature/ambient temperature**

The term “ambient temperature” is outdated due to lack of consensus or a defined temperature. Whenever mentioned, the term means “room temperature” to be stored at 15°C - 25 °C or up-to 30 °C at the most (storage-area should be clean, dry and ventilated).

### **Cold Supply Chain**

#### **Temperature Control of Raw Material**

The manufacturer is responsible for ensuring the stability of manufactured dosage. Temperature, light, air, humidity and specially packaging are the main stability parameters. Stability-testing needs to be conducted on real-time temperature and relative-humidity representing storage conditions as experienced in the chain of distribution of different climatic-zones across the world (Madsen, Cherris, Shabushnig, & Hunt, 2005).

Mischler (2002) stated that multinationals are defining new conditions of stability-testing for the global market. For which they test stability at 50 °C & with 75% RH. The concept behind this is to recommend a lower shelf life when exposed to higher ambient temperatures. It has been also observed that drugs packed in blister-packing gained moisture at higher rate when compared to drugs having striped packing (Bajaj, Singla, & Sakhuja, 2012).

#### **Packaging & Labeling of Temperature Sensitive Medicine**

As discussed earlier, protecting a temperature-sensitive medicine from heat declension is gaining importance as the number of biopharmaceutical products are increasing and authorities look for evidence of product-stability throughout the chain.

Considering the need for protecting against excessive temperatures, DHL (a well known logistics company) has introduced DHL Medical Express in 2012 to support the specific transportation needs for temperature-sensitive medicines/vaccines from research centers / manufacturers to the final consumers. The company offers a comprehensive variety of packaging alternatives you can select from; different box sizes within each heat-variety-range allows selection of the most efficient solutions whilst guaranteeing heat-variety precision and stability (DHL Express, 2012).

WHO (2009) specifies a storage space declaration based on the label of finished product. Wherever appropriate, specific guidelines need to be provided, particularly if the product is vulnerable to cold-temperatures. There should also be an immediate link between the storage space declaration on the brand and the finished product. An expiry date also needs to be shown on the packaging label. Thus temperature sensitive packaging helps to guarantee that the products are shipped safely and at the precise temperatures.

#### **Temperature Control in Transportation & Distribution**

Transportation and distribution play perhaps the most important role in protecting the integrity of the product (Taylor, 2006). Good distribution practices need to be followed in

order to prevent an entry of any counterfeit medicines. Moreover, the temperature of storage cabin/container in the transportation of medicine is just as important and needs not to be confused with leaving personal-use medicine in the boot of one's car. For longer a duration of transport, such as inter-city distribution, refrigerated Lorries need to be used to prevent exposure from excessive temperatures (Fudge, 2009). Where special storage-space conditions are specified by the manufacturer, it should be examined, and supervised. Temperature controlled storage, first-in first-out (FIFO), and good warehousing practices help reduce the risk involved in transportation and distribution (Fudge, 2009).

### **Problems in Protecting Temperature Sensitive Medicines in Pakistan**

The pharmaceutical supply-chains in Pakistan face many problems, since regulatory controls in the country are rather lax and corruption matured. As a result, retailing in pharmaceutical sector is largely carried out like grocery-store retailing; anyone can open a chemist's shop. This part of pharmaceutical supply chain is largely to be blamed for break in the cool chain, since most chemists do not have refrigerators, which are required to prevent degeneration of various medicines. Moreover, hours and hours of load-shedding (sometimes extending upto 10-18 hours) makes the refrigerators useless anyway.

Governmental vaccination campaigns are often funded by donor agencies, which have sufficient resources to maintain a cool chain but due to poor management and lack of training the result often leads the vaccination campaigns to failure.

WHO (2009) has identified the lack of infrastructure in maintaining a cold supply chain as one of the major problems leading to failure in immunization of children against polio, measles, MMR, and Rubella; whereby they claim that one of the biggest problems that Pakistan faces today is the lack of infrastructure in Cold Chain Logistics. WHO also further identified load shedding and poorly educated staff are also the factors accountable for mismanagement of the medicines from extreme temperatures (Suhail, 2012).

### **Hypotheses**

The literature reviewed as above emphasized the importance of maintaining appropriate temperatures to protect the efficacy of pharmaceutical products. Medicines are imported from varying countries and mishandling during shipments can very well reduce the potency of the raw materials. Most large pharmaceutical companies have their own laboratories and inspect the raw-materials before formulation.

Transportation within the country can take up-to three days of travel time and as ambient temperatures can raise upto 45° C and the temperatures inside the storage compartments can be even higher. Protecting the medicine in this case and time is particularly very important. Therefore, products must be transported within temperature controlled transport and a record of changes in temperature throughout the transport can further be monitored and recorded to better protect the efficacy of medicinal products.

The last stage is perhaps that of the actual distribution of the shipment to its destination, which in logistics is known as the "last mile". Trucks are the prime modes of transportation at this stage and must meet the necessitated cold chain requirements.

Maintenance of the desired temperature at the Chemist is the key to the completion of cold supply chains. It is however also the weakest link in the chain.

Following hypotheses have been formulated for this study

**H<sub>1</sub>:** Ensuring temperature-control of active-ingredients during shipments is positively related to efficacy of imported medicine

**H<sub>2</sub>:** Appropriate temperature-control of stored raw-material and finished-product is positively related to protecting efficacy of the medicine

**H<sub>3</sub>:** Maintaining appropriate temperature and cool chain from manufacturing to delivery and eventually to the patients, is positively related to protecting efficacy of the medicine.

### Research Method

The data was collected using a questionnaire-based survey using 5 point likert scale, which ranges from agreement to disagreement level to a given statement. The sampling technique was un-restricted non-probability technique due to time constraints and availability of the pharmaceutical professionals dealing in medicines management. The respondents were limited to professionals in pharmaceutical organizations as per the need of this study. The sample size was 280 respondents and it was self-administered questionnaire survey to avoid in-accuracy of the data collection.

### Statistical technique

For investigating the propositions of this study one sample t-test was deployed while keeping critical value of acceptance equals to 4 (i.e. agreed with the statement) for accepting or rejecting the hypotheses.

### Results

All the 3 hypotheses were used to study the factors affecting efficacy of temperature sensitive medicines. Primary data from 280 respondents revealed all 3 hypotheses.

Table 2 presents the one sample t statistics showing the mean for hypotheses is greater than four, indicating acceptance of the hypotheses.

**Table 2: One sample t-test**

	N	Mean	Mean Difference	t	Sig. (2-tailed)
<b>H1:</b> Ensuring temperature control of active ingredients during shipments is positively related to the efficacy of imported medicine.	280	3.735	-0.2647	-2.803	0.006
<b>H2:</b> Appropriate temperature control of stored raw-material and finished product is positively related to protecting efficacy of the medicine	280	4.431	0.43137	5.195	0
<b>H3:</b> Maintaining appropriate temperature cool-chain from manufacturing to delivery to the patients is positively related to protecting efficacy of the medicine	280	4.156	0.15686	1.702	0.092

One-sample-statistics (Table 2) shows a mean value of 3.73 for hypothesis-1 while hypotheses H2 and H3 have values of 4.43 and 4.15. This shows acceptance of hypotheses H2 and H3; while for H1, the value is significantly different than the critical value of acceptance. Thus, we failed to accept the H1.

The reason for rejection of H1 is that any deterioration in purity of raw material can be adjusted at formulation stage and therefore, the respondents did not consider it as having a large impact on the efficacy of finished-product.

### **Discussions, Conclusion, Policy Implications and Future Research**

The healthcare sector of Pakistan is widely rooted with many problems. Government funding for the health sector merely remains poor. The quality of healthcare at public hospitals is so poor that many people very well prefer to bear all of their medical care costs themselves, instead of availing the “free treatment” at a public-hospital (whereby patients are often asked to buy expensive medicines themselves). Unfortunately, the medicines are often substandard, counterfeit, expired, or have lost their potency due to exposure to excessive temperature during storage and transportation (often the case for temperature-sensitive medical products).

Ordinary people spend their hard-earned savings on buying medicines that have already deteriorated enough to be of any medicinal value. Normal medicines, available at chemists require storage at around 25 °C, although the ambient temperature during the summer ranges from 40-45 °C. Thus most medicines, left up in the shelves at “ambient temperatures”, degenerate on a continuous basis and lose potency overtime as they lay exposed to high temperatures. These chemist stores therefore, need to be maintained with air temperatures at about 25 °C, if the efficacy and potency of the shelf-medication is to be sustained.

Medicines that require 4-8 °C temperature are stored in refrigerators, however, refrigerators are not much of a help in places where 10-12 hours of power black-outs are a common occurrence. Therefore, regulatory actions are required to protect the interests of the public and particularly patients; whereby the major pharmacy outlets, such as Kausar Medicos and Islamabad Medicos need to be required of equipping their stores with temperature maintenance and monitoring.

The government should seriously take measurements and deployment for proper storage spaces for medicines all across the country, which are especially a part of the national pharmaceutical association: Pakistan Pharmaceutical Manufacturing Association (PPMA). The outlets must thereby be made to conform to the standards: be equipped with standby power-supply, maintain premises temperature at 25 °C for routine shelf storage and maintain refrigerated-storage for frozen and 4-8 °C-storage for specialty-medicine, when required. Moreover, since the value of medicine sold nationwide was estimated to be at \$3.2 billion (Rs 330 billion) in 2014 Pakistan Pharmaceutical Manufacturers’s Association [PPMA] (2014); these kind of assets need to be safeguarded well. A reputation of spurious drugs due to mismanagement with regard to transport and storage and infiltration of counterfeit drugs is not going to help the pharmaceutical sector. Maintenance of cold chain in transportation, storage, and retail is one of the major interests of pharmaceutical sector as the reputation for safe and effective medication is perhaps the most valuable asset to have for the pharmaceuticals themselves. Thus, professionally well-managed pharmacies with support from government and the pharmaceutical sector are both in the interest of the entire sector and the consumers.

The set-up like that of the Boots (UK) can also be widely adopted in Pakistan. It may not require heavy-scale funding from any of the agencies or the pharmaceutical sector as almost all major supermarkets already operate with well-maintained chemist sections. As a

last measure, the government needs to refrain from allowing licenses to chemists who do not meet the minimum standards of storage and maintenance of environment as necessitated by the nature of the medicines.

The research highlights the need of involving pharmaceutical sector and regulatory bodies to ensure that the retail outlets are professionally maintained and managed. Throughout the developed world, chemist shops are commercially viable even when they are run under strict standards to better protect the efficacy of temperature sensitive medicines.

Financial viability of professionally managed chemist outlets needs to be determined. Although we may speculate that it is rather commercially viable in large cities. In smaller towns and villages however, chemist shops may require support from the pharmaceutical sector. For temperature sensitive products requiring storage at low temperatures, courier services can be a viable option and specialize in delivery of temperature sensitive medicines.

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