

**Research Article****Last Mile Delivery of Cold Chain Medicines – Challenges and Recommendations**

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ABSTRACT

Cold chain medicines are those that require special temperature-controlled cold storage to maintain their quality and efficacy. Cold chain management is important to ensure that the right quality is maintained throughout the supply chain. There lies a variety of reasons why cold chain management continues to be the challenge in India like lack of the consolidated list of cold chain medicines, lack of standard refrigeration guidelines for retail pharmacies, non-uniformity in storage temperature instructions on the label, patient education and lack of awareness. The study aims to identify the challenges faced in the last mile delivery of such medicines in India and suggest practical recommendations for improvement that confirms the international best practices. More than 100 interviews were conducted with healthcare professionals like doctors, pharmacists, retail pharmacy experts, logistic partners, distributors and ex-regulators to understand the storage conditions and the possible solutions, especially at retail and customer level. An exhaustive list of cold chain medicines was framed with the databases of Indian hospitals, local drug distributors and drug retailers. Given the complexity of cold chain system in India, the guidelines for maintaining and managing the cold chain should be clearly available and then be mandatorily followed, in order to avoid the deleterious effects on such medicines due to storage and handling issues as elaborated in this study.

Introduction**What are Cold Chain Medicines?**

Cold chain medicines are those that requires special temperature-controlled cold storage to maintain their quality and efficacy. A cold chain is an uninterrupted series of storage and distribution activities that maintains products at a required temperature range of 2°C and 8°C or between -10°C and -20°C as per their requirements [1].

Why is Cold Chain Management important?

Cold chain management is important to ensure that the right quality is maintained throughout the supply chain. There are standardized guidelines around the world focusing on the right storage and transportation, and adhering to these standards amidst varied climatic conditions is a huge challenge. Cold

chain products are sensitive biological substances that can become less effective or lose their potency if not stored properly. So it is important that the right temperature is maintained throughout the distribution chain, starting from the dispatch of the product from the manufacturing site to when it reaches the patient [1].

What is the Cold Chain Medicines market size in India?

As per the AWACS data for the year 2016-17, the cold chain medicines contributed more the 6000 crores to the Indian pharma market which is roughly around 6% of the total Indian pharma market. While a great emphasis is put on the control and monitoring for storage and transport conditions from the manufacturers to the wholesalers, a lot of work has still to be done for the very 'last mile' distribution steps [2].

What is Cold Chain breach?

Cold chain breaches are defined as temperature variations outside of the range of 2°C to 8°C lasting for more than 15 minutes. The effectiveness and shelf life of a product greatly diminishes on being exposed to conditions beyond the required temperature range. There lies a variety of reasons why cold chain management continues to be challenge in India like lack of consolidated list of cold chain medicines, lack of standard refrigeration guidelines for retail pharmacies, non-uniformity in storage temperature instructions on label and patient education and lack of awareness [3].

Objectives of the study

The study aims to identify the challenges faced in the last mile delivery of such medicines in Indian system and suggest practical recommendations for improvement that conforms the international best practices.

Methodology

We conducted ~100 interviews with doctors, pharmacists, retail pharmacy experts, logistic partners, distributors and ex-regulators to understand the gaps and the possible solutions for the cold chain maintenance especially at the retailer and consumer level. Besides this, an exhaustive research and literature review was carried out to identify the medicines that require cold chain storage. There is also enlistment of identified comprehensive list of cold chain medicines by referring to database of multiple hospitals, distributors and retailers available in India including AIOCD, AWACS database, 1mg drug database and then mapped it to a list of ~174 salts with more than 2500 SKU's to arrive at a final list

Challenges associated with the cold chain in India

It is crucial to continuously monitor and maintain the cold chain in order to keep the pharmaceutical product's efficacy intact. For which, it is imperative to have an undisrupted, seamless and smooth functioning supply chain, however, it is not that easy in the Indian market and the concerned stakeholders face several challenges.

Lack of a consolidated list of cold chain medicines

The Drugs and Cosmetics Act 1940 defines the life periods of drugs and conditions of storage under Schedule P but lacks a comprehensive list of medicines that require temperature regulation with clear storage instructions with upper and lower limit [4]. Many retailers and consumers believe that only insulins, vaccines and hormonal preparations require temperature control, but there are several other drug categories which do require temperature control. A consolidated list of such medicines reviewed by stakeholders including pharmacists, industry experts, registered medical practitioners, manufacturers and the regulators, can serve as a reference for retailers. The information or the list available internationally will not be of much help for Indian setting as there is lot of variations in climatic conditions and also the medicines used

Lack of standard refrigeration guidelines for retail pharmacies

The medicines are stored in the same refrigerators as food and drinks with continuous opening and closing of refrigerators hampering the temperature maintenance. The refrigerators usually have insufficient space preventing the air to circulate freely and are also found to have insufficient ice packs with less space in freezers to cater the need of proper transport and delivery of cold chain medicines [5]. There is also lot of ambiguity where to store the medicine in the refrigerator (inside the freezer or outside). Most of the retail pharmacies are equipped with domestic refrigerators which are not prepared for contingencies like maintenance, defrosting, power failures, and temperature monitoring.

Non-uniformity in storage temperature instructions on label

The storage instructions on medicines are not well-written and ambiguous at times. Many pharmaceutical products do not carry any temperature instructions, while some products carry different instructions.

Some of the challenges being faced are [6]:

- Some products do not carry any storage instruction.
- Some products carry storage instruction like “*store at room temperature*”.
- The room temperature across the country varies and also varies according to the time of the year.
- Some products carry storage instruction as “*store in cool place*”, but the temperature range is not specified.
- Some products carry instructions as “*store in cool place below 25 C*”.

So, such serious variations in labeling can be misleading and may make the last mile delivery of such specific medicines more challenging.

Last mile challenge in the delivery of cold chain medicines for retailers and consumers

While a great emphasis is put on the control and monitoring for storage and transport conditions from the manufacturers to the wholesalers, a lot of work has still to be done for the very ‘last mile’ distribution steps. The last mile is the end stage in the logistics chain where a shipment meets its ultimate destination. In pharma world it means from the manufacturer of the cold chain medicine to the patient. There is a lack of knowledge on the cost effective options for last mile delivery of cold chain medicines [7].

Patient awareness and education

There is a major requirement to make patients and co-habitues aware and also educate the patients on how their medicines have to be stored in compliance with the cold chain guidelines and the potential risks of temperature breach. Patients also lack the knowledge on how to transport and store their cold chain medicines while moving outdoors.

Recommendations

Listing of cold chain medicines in the billing software

- We have compiled a comprehensive list of cold chain medicines through extensive research and referring to database of multiple hospitals, distributors and retailers (Ref Appendix – III, IV).
- Tagging cold chain medicines in the billing software used by retail pharmacies will provide more clarity and easy bifurcation between a cold medicine and a normal medicine. For this, the regulators should make it mandatory for all retailers to have a billing software with all cold chain medicines marked so as to identify which medicines demand a cold chain storage and transport.
- The technology would also enable retail pharmacies to educate customers (e.g. by SMS alerts) regarding storage requirements of a particular cold chain medicine.

Refrigeration guidelines for cold chain medicines

Guidelines that conform with the WHO guidelines should be enforced [4]:

Refrigerators at retail pharmacies

- Refrigerators that open on the top are more efficient than vertical ones as hot air rises while cold air falls.
- Maintain frozen icepacks in sufficient quantity to transport items that require cold storage in cold boxes.
- Refrigerators and freezers should be placed at least at an arm length away from the wall, and also with sufficient in between space in case of multiple refrigerators and/or freezers placed in a room; this will increase the air circulation.
- Under ideal conditions, rooms with multiple refrigerators and/or freezers should have air conditioning as refrigerators and freezers generate large amount of heat which can damage the equipment over time. If it is not possible to have air conditioning, fans should be installed around the equipment to increase airflow also ensuring the air flow in spaces behind the refrigerators.
- Must be designed specifically for that purpose, must not be used to store food, blood, milk, drink or specimens (domestic refrigerators are not suitable for this purpose).
- Must be of appropriate size for the quantity of stock to be stored (stock should not occupy more than 50% of space to allow adequate air circulation). Order frequency should be increased rather than compromising with the air flow by filling the refrigerator.
- Must be defrosted every 6 to 8 weeks in case it is not self-defrosting.
- Its integral thermometer should be calibrated at least annually to ensure true readings.
- Must have an independently powered digital maximum and minimum thermometer which records the current temperature, regardless of the existence of integral refrigerator thermometer.

- Must be regularly serviced according to manufacturer's instructions to ensure its proper functioning [5].

Transporting Refrigerated Medicines

- Suitable rigid containers should be used all the times to reduce damage to medicines during transit.
- Temperature should be maintained based on the cool box and type of gel pack used; some commercial icepacks/gel packs contain a chemical product ensuring that icepack remains colder than normal water-filled icepacks.
- Nowadays, ice boxes with sensors and temperature logger are also available that accurately records the temperature within the ice box, and should be considered whenever feasible [5].

Storage while transit and after delivery

- Upon arrival, medicine should be transferred to refrigerator immediately.
- For overnight storage of medicines, a dedicated refrigerator or an electric portable storage unit that maintains the required temperature should be used.
- The consumers must be instructed to store medicine in refrigerator immediately until usage and then should be placed back to refrigerator immediately after drawing up each recommended dose [5].

Standard temperature instructions (Refer to Appendix I)

The research indicated that there is an urgent need for stringent and uniform temperature instructions throughout the country. The regulatory authorities should provide unambiguous storage temperature instruction guidelines on the medicine label, also mentioning mandatory proper storage in the required temperature condition. Exact temperature range should always be specified on the labels like store in a cold place at +2°C to +8°C and do not keep in a freezer. Some of the points to ponder about the labelling information regarding temperature are:

- a) Exact temperature needs to be mentioned.
- b) Both upper and lower temperature range with exact temperature range needs to be mentioned.
- c) The temperature range needs to be consistent on all active molecules, same drug. Should not be different for different batch numbers.
- d) Exact temperature range (instead of “cool”, “cold”, “room temperature”) should be defined and labeled.

Safeguarding during power outage

In the event of power outage, a number of steps should be taken to minimize damage to the pharmaceutical products:

- a) The time of power outage should be noted.
- b) The refrigerator and freezer doors should not be opened during power outage.
- c) If the power outage continues for more than 24 hours than the products stored in freezer should be removed and packed

in dry ice. Ensure adequate amount of dry ice availability all the times.

d) When the power is restored, the temperature in the refrigerator and freezer should be recorded, and monitored until the temperature returns to the desired temperature [5].

These allows calculation of the time duration for which the product was stored beyond the desired temperature and hence, enabling risk assessment calculations of continued potency of the involved pharmaceutical product/s [8].

Last mile challenge in the delivery of cold chain medicines

There are various options available like vaccine carriers, cool boxes and gel packs depending on the time of cold chain required. Given the complex supply chain the manufacturer have little visibility on the last mile of the medicine as it reaches chemist shelves and finally to patients. The last mile is the most vulnerable point and still remains as the most unsolved issue of the supply chain. (Refer to Appendix II)

Patient education

The patient needs to be informed regarding the storage requirements of all cold chain medicines, an automated sms must be sent to the patient once a cold chain order is delivered or handed over to customer. The use of technology will enable this service once a medicine tagged as a cold chain medicine is sold from a retail pharmacy. Standard tips for the use of insulin can be written on all insulin products, some of instructions for the use of insulin products are as follows:

- Insulin should be kept in the refrigerator between +2°C to +8°C. Do not keep in the freezer.
- If you are using an insulin pen, you may store it outside refrigerator at room temperature not exceeding 30°C.
- Never expose the product/s to direct heat or sunlight.
- Check the label for the number of days it can be used after opening.

Appendix – I

Temperature Standards

The Indian Pharmacopoeia [10]	<ul style="list-style-type: none"> ● Store in a dry, well-ventilated place at a temperature not exceeding 30° ● Store in a refrigerator (2° to 8°). Do not freeze. ● Store in a freezer: (-2° to -18°) ● Store in a deep freezer: (Below -18°)
Definitions in the WHO Guidance [9]	<ul style="list-style-type: none"> ● Store frozen: transported within a cold chain and stored at -20°C (4°F). Store at 2°-8°C (36°-46°F): for heat sensitive products that must not be frozen. ● Cool: Store between 8°-15°C (45°-59°F). ● Room temperature: Store at 15°-25°C (59°-77°F). ● Ambient temperature: Store at the surrounding temperature. This term is not widely used due to significant variation in ambient temperatures. It means "room temperature" or normal storage conditions, which means storage in a dry, clean, well-ventilated area at room temperatures between 15° to 25°C (59°-77°F) or up to 30°C, depending on climatic conditions.

Limitations of the study

While the study aims at targeting day today operational issues faced at the retailer and consumer level while maintaining the cold chain process, the study has the following limitations.

- The study only refers to the challenges faced by some of the supply chain stakeholders and it fails to address the issues faced at the manufacturing units for handling of such medicines.
- The study does not evaluate the major public health issues pertaining to delivery of cold chain medicines in Indian Health care system.

Conclusion

Addressing the cold chain delivery system of medicine is the utmost need of hour especially under varied environmental and climatic conditions that our country possess. Given the complexity of cold chain system, the guidelines for maintaining and managing the cold chain should be clearly available and then be mandatorily followed, in order to avoid the deleterious effects on such medicines due to storage and handling issues as elaborated in this study. We would also recommend building further on this and making it a robust and technology based process in the Indian Health care setting.

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The U.S. Pharmacopeia [9]	<ul style="list-style-type: none"> ● Cold: Any temperature not exceeding 8°C (46 °F). ● Cool: Any temperature between 8° and 15° (46° and 59 °F) ● Room temperature: The temperature prevailing in a work area. ● Controlled room temperature: The temperature maintained thermostatically that encompasses at the usual and customary working environment of 20°-25° (68°-77 °F). ● Warm: Any temperature between 30° and 40°C (86° and 104 °F). ● Excessive heat: Any temperature above 40° (104 °F).
The European Pharmacopoeia [9]	<ul style="list-style-type: none"> ● Deep-freeze: below -15°C ● Refrigerator: 2°C to 8°C ● Cold or cool: 8°C to 15°C ● Room temperature: 15°C to 25°C.
The Japanese Pharmacopeia [9]	<ul style="list-style-type: none"> ● Cold: 1°C - 15°C ● Standard temperature: 20°C ● Ordinary temperature: 15°C - 25°C ● Room temperature: 1°C - 30°C ● Lukewarm: 30°C - 40°C

Appendix – II Last Mile Cold Chain Delivery

Last mile cold chain delivery [6]

Insulation options		Cooling agents/device	
Cold boxes	Vaccine carriers	Water packs/ice packs	Gel packs
Depending on the model, cold boxes can be used to store these medicines for periods of up to two days or more [8].	Current prequalified carriers have a cold life with frozen ice packs of between 18 and 50 hours at +43 °C [8].	Water packs are flat, leak-proof plastic containers that can be filled with tap water. They are used to line the inside of the cold box or vaccine carrier. Water packs are used to keep medicines at the required temperature range inside cold boxes and vaccine carriers [8].	Gel packs has the advantages of ease of use and storage, with the added benefit of being reusable if so desired. Additionally, the product that the gel pack is keeping cold will not get wet like it would with wet ice, as the refrigerant gel is sealed into a plastic pouch [8].
Cold life without openings at +43 °C for 2hrs-8hrs depending on ice packs used [8].	Cold life without openings at +43 °C for 10 hrs – 20 hrs depending on the ice packs used [8].	The water packs will stay frozen from 24-36 hours in an insulated container, At room temperature can keep the cold chain for about 3-4 hours depending on the insulation [8].	The gel packs will stay frozen from 36-48 hours in an insulated container, At room temperature can keep the cold chain for about 10-20 hrs depending on the insulation [8].
Recommendations			
1 litre (minimum 2 icepacks / gel packs of size - 185 x 90 x 22mm)	0.80 Litres (equipped with slots for 4 standardized ice packs)	Use standardized and proper insulated cool box, ice packs to be used in proper consistency (non reusable)	Use standardized and proper insulated cool box, ice packs to be used in proper consistency (reusable)
3 litre (minimum 4 icepacks / gel packs of size - 185 x 90 x 22mm)	2.46 Litres (equipped with slots for 4 standardized ice packs)		
Cost - Rs 100 - Rs1500 (approx depending on the size)	Cost - Rs 600 - Rs 8000 (approx depending on the size)	Cost - Rs 2 - Rs 20 (approx depending on the size)	Cost - Rs 15 - Rs 100 (approx)

Appendix - III

Recommended list of cold chain medicines form wise

Salt	Drug Form	Salt	Drug Form
Abatacept	Injection	Daptomycin	Injection
Abciximab	Injection	Darbepoetin alfa	Injection
Adalimumab	Injection	Denosumab	Injection
Albumin	Injection	Diltiazem	Injection
Alprostadil	Injection	Dinoprostone	Gel, Pessaries
Amphotericin B	Injection	Docetaxel	Injection
Anti Rh D immunoglobulin	Injection	Doxorubicin (Liposomal)	Injection
Aprotinin + Fibrinogen + Thrombin	Injection	Dulaglutide	Injection
Asparaginase	Injection	Epirubicin	Injection
Atracurium	Injection	Eptifibatide	Injection
Becaplermin	Gel	Erythropoietin	Injection
Bevacizumab	Injection	Etanercept	Injection
Bleomycin	Injection	Fibrinogen	Injection
Botulinum Toxin	Injection	Filgrastim	Injection
Botulism Sera	Injection	Follicle Stimulating Hormone(FSH)	Injection
Calcitonin	Injection, Nasal Spray	Fosphenytoin	Injection
Calcium Folate	Injection	Glatiramer Acetate	Injection
Carboprost	Injection	Glucagon	Injection
Caspofungin	Injection	Glutathione	Injection
Cetrorelix	Injection	Goserelin	Injection
Cetuximab	Infusion	Human Chronic Gonadotropin Hormone	Injection
Corticotropin	Injection	Human Gamma Globulin	Infusion
Cyclophosphamide	Injection	Human immunoglobulin	Injection
Dacarbazine	Injection	Human Normal Immunoglobulin	Infusion
Ifosfamide	Injection	Polyvalent Immunoglobulins Combination Modulation	Infusion
Infliximab	Injection	Poractant Alfa	Injection
Interferon Alpha 2A	Injection	Pemetrexed	Injection
Interferon Alpha 2B	Injection	Proparacaine	Eye Drop
Interferon Beta-1A	Injection	Recombinant Human Epidermal Growth Factor	Gel
Latanoprost	Eye Drop	Risperidone	Injection
Leuprolide/leuprorelin	Injection	Rituximab	Injection
Liraglutide	Injection	Rocuronium	Injection
Lixisenatide	Injection	Sirolimus	Injection
Lorazepam	Injection	Sodium Hyluronate	Injection
Luteinizing Hormone	Injection	Somatostatin	Injection
Menotropins	Injection	Somatropin	Injection
N-butylcyanoacrylate	Injection	Streptokinase	Injection
Nicorandil	Injection, Tablet	Succinyl Choline Chloride	Injection
Nimotuzumab	Injection	Tenecteplase	Injection
Octreotide acetate	Injection	Teriparatide	Injection
Pancuronium	Injection	Terlipressin	Injection
Pegfilgrastim	Injection	Trastuzumab	Injection
Pegylated Interferon Alpha 2A	Injection	Triptorelin	Injection
Pegylated Interferon	Injection	Urofollitropin	Injection

Alpha 2B			
Peliperidone	Injection	Vasopressin	Injection
Hyaluronic acid	Injection		

Note: All the vaccines and insulin's are categorized under Cold Chain Medicines list

Appendix - IV

Recommended list of cold chain medicines as per group

Antimicrobial	Amphotericin B, Caspofungin injection, Daptomycin injection
Anticancer	Asparaginase, Bevacizumab, Bleomycin, Cetuximab, Cyclophosphamide injection, Dacarbazine, Docetaxel, Doxorubicin (Liposomal), Epirubicin, Ifosfamide, Leuprolide/leuprorelin, Nimotuzumab, Pemetrexed, Rituximab, Trastuzumab
Anti-diabetics	Insulins, Dulaglutide, Liraglutide, Lixisenatide
Biologics	Anti Rh D immunoglobulin, Human Gamma Globulin, Human immunoglobulin, Interferon Alpha 2A, Interferon Alpha 2B, Interferon Beta-1A,, Human Normal Immunoglobulin, Glatiramer Acetate, Adalimumab, Etanercept, Infliximab Abatacept, Pegylated Interferon Alpha 2A injection, Polyvalent Immunoglobulins Combination Modulation
Hematological products	Abciximab, Albumin, Aprotinin + Fibrinogen + Thrombin, Darbepoetin alfa, Eptifibatide, Erythropoietin, Filgrastim, N-butylcyanoacrylate, Pegfilgrastim, Streptokinase, Tenecteplase, Terlipressin
Bone related	Calcitonin, Denosumab, Hyaluronic acid inj, Sodium Hyluronate inj, Teriparatide
CNS	Fosphenytoin, Lorazepam injection, Risperidone inj, Paliperidone inj
CVS	Diltiazem, Nicorandil
Respiratory	Poractant Alfa
Dermatological	Becaplermin(Recombinant Platelet Derived Group Factor), Recombinant Human Epidermal Growth Factor
Hormones	Cetrorelix, Corticotropin, Follicle Stimulating Hormone(FSH), Luteinizing Hormone, Glucagon, Goserelin, Menotropins, Octreotide acetate, Somatostatin, Somatropin, Triptorelin, Urofollitropin, Vasopressin, Human Chronic Gonadotropin Hormone (HCG)
Skeletal Muscle relaxant	Atracurium, Pancuronium, Rocuronium, Succinyl Choline Chloride
Prostaglandin	Alprostadil, Carboprost, Dinoprostone, Latanoprost*
Miscellaneous	Botulinum Toxin (botox), Botulism Sera, Proparacaine, Sirolimus inj

Note 1: All the vaccines and insulin's are categorized under Cold Chain Medicines list.

Note 2: *Other ophthalmic preparations like bmatoprost, travoprost can be stored between 2° to 25°C.

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