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Comparative Account of Diverse Regulatory Guidelines for Storage and Transportation of Pharmaceuticals

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Abstract: Good Pharmaceutical Storage and Distribution Practices (GS&DP) are the component of Quality Management System (QMS) that promises the quality of the pharmaceuticals through controlling various activities allied to storage and distribution operations procedures. There are a number of International Regulatory Guidelines, which toss light over the requirement, and importance of Quality and Quality Assurance. Pharmaceutical products require controlled storage and transit conditions in order to ensure their quality. Poor regulatory controls over the interstate transportation and warehousing complicate the matter impacting the product quality, efficacy and safety. Indian drug regulatory guidelines are inadequately defined and thus the impact of varied climatic conditions during transport and warehousing is still not appropriately evaluated and studied. These can have serious repercussion on the physical, chemical and microbiological attributes of the drug product. The present study intended for comparing the regulatory guidelines of other countries and agencies with Indian regulatory standards and the need to improvise the latter to bring under purview the measures that can prevent the product instability. Further, based on the evaluation studies on certain model pharmaceutical products, suggestive evaluation methodologies will be proposed from Indian perspective to account for the go-ahead changes a product undergoes during the supply-distribution channel, which the manufacturer needs to assess and furnish to the central drug regulatory agency such as DCGI prior to getting marketing approval.
Keywords: - Regulatory guidelines, Storage, Transportation , Quality, Pharmaceuticals.

Introduction

In the recent years globalization of development and production of pharmaceuticals has increased manifolds. Besides the opportunities like cost saving and enhancement of global availability of medicines, globalization poses new challenges for the quality of medicinal products. Complex supply chains complicate communication, increase the demands for technical agreements and facilitate the potential of counterfeit medicinal products. Of growing importance in the context of globalization are also the requirements on packaging material, stability of the products and precautionary measures during transport (controlled transport, transport validation) due to long transportation routes for pharmaceuticals, bulk and finished products through

different climatic zones. Increased shifting of production sites elevates the relevance of technological and method transfer.

Pharmaceutical industry and competent authorities have to accept these challenges. Global collaboration and harmonization are playing a decisive role in establishing appropriate approaches for the problems which accompany globalisation. Science, risk based approaches and decision making techniques are valuable tools to deal with these complex challenges. The extent to which drug substances, bulk products and final products are stored and transported is increasing with supply chains becoming more complex due to globalisation. The goods might even pass different climatic zones during transportation. Environmental conditions during transport like temperature, humidity or light might adversely affect the quality of drug substances. The worst case scenario of such quality deterioration would be harm to the patient. This might occur if the quality damage impacts safety or efficacy and was not detected before reaching the patient. Deviations from transport conditions thus might necessitate their disposal which means a financial damage for the company as well a national loss. As a consequence high attention must be given to temperature and humidity conditions during transport. Further relevant matter in context of increasing transport of pharmaceuticals, is the supply chain security and traceability to prevent counterfeits.

Regulatory Situations Concerning Transport Conditions:-

Regulatory requirements and guidance on transport conditions of medicinal products are found on international level in WHO guidance documents, on European level in the EC (European Commission)-GMP guide, the "Guidelines on Good Distribution Practice" and the CHMP guideline "Guideline on Declaration of Storage Conditions" and on national level there are country specific guidelines.

In Germany requirements are defined in the AMWHV. As the requirements of the EC-GMP guide and requirements from AMWHV are superficial, they are of little help in practice. The "Guidelines on Good Distribution Practice" (GDP) is currently under revision. The new version which was released for public consultation in July 2011 includes more specific guidelines than the previous version.

More detailed guidance is given in WHO guidance documents, the USP monograph <1079>, the Canadian guideline "Guidelines for Temperature Control of Drug Products during Storage and Transportation" and in the guideline of the Irish Medicines Board (IMB) "Guide to Control and Monitoring of Storage and Transportation Temperature Conditions for Medicinal Products and Active Substances". The requirements defined above mentioned documents are summarized in the subsequent paragraphs.For India, it has reference in form of schedule M of the Drugs and Cosmetics Act 1940, and Rules 1945.

WHO Guidelines

There are several guidance documents issued by the WHO, which are applicable to medicinal products which cover transportation and storage from finished product manufacturers to pharmacies [1-3]. While the "WHO guides for storage practice for pharmaceuticals" [1] also covers starting materials and bulk drug products these are out of scope of "WHO good distribution practice for pharmaceutical products" [3] but covered by the "Good trade and distribution practices for pharmaceutical starting materials" [2]. The following provisions are made in the WHO guidance documents which are regarded together due to the high degree of overlapping with regard to transport conditions: During transportation integrity of the package should be ensured and if special storage conditions are stated on the label of the product these have to be maintained. This means, if the expected environmental conditions deviate from the storage conditions defined, transportation should be performed at controlled conditions, which includes checking, monitoring and recording the temperature/humidity conditions with calibrated devices.

The storage conditions and labelling statements are defined in the WHO guidance documents as reproduced in Table 1 .WHO, Stability testing of active pharmaceutical ingredients and finished pharmaceutical products [1-4]. The labelling statements in the WHO guidance documents deviate between the guidance documents. As the "WHO guides for storage practice for pharmaceuticals" is older than the guide on "Stability testing of active pharmaceutical ingredients and finished pharmaceutical products" it is assumed that the labelling statements given in the first guide are partially out-dated and are therefore displayed in brackets in Table 1. The designation of labelling statements differs from the approach used in Europe, where a special

labelling statement is not required if the stability data at accelerated conditions are within the specification over 6 months of storage.

Table 1 Storage Conditions According to WHO Guidance Documents [1,4].

Testing conditions where the product is stable	Required labelling statement	Storage/transportation temperature
Not available	Without labelling statement	15 – 25^{0}C or 15 - 30^{0}C (depending upon climatic conditions)
25^{0}C/60% RH (long term) 30^{0}C/65% or 75% RH (long term)	Do not store above 30^{0}C	2 – 30^{0}C
25^{0}C/60% RH (long term) 40^{0}C/75% RH (accelerated) or 25^{0}C/60% RH (long term) 30^{0}C/65% RH (intermediate, failure of accelerated)	Do not store above 25^{0}C	2 – 25^{0}C
Not available	Do not store above 15^{0}C	2 – 15^{0}C
5^{0}C ± 3^{0}C (long term) 30^{0}C/65% or 75% RH (long term)	Store in a refrigerator (2 - 8^{0}C) or Do not store over 8^{0}C	2 – 8^{0}C
Not available	Do not store below 8^{0}C	8 – 25^{0}C
-20^{0}C ± 5^{0}C	Store in a freezer	Not available
Not available	Protected from moisture	≤ 60% RH moisture resistant container
Not available	Protected from light	Light-resistant container

EU Guidelines

The EC-GMP Guide, Volume 4 Part II defines some requirements for drug substances with regard to storage and transport in paragraphs 10.21 to 10.23. According to that, drug substances "should be transported in a manner that does not adversely affect their quality", "the transport conditions should be stated on the label" and "the manufacturer should ensure that the contract acceptor (contractor) for transportation of the drug substance or intermediate knows and follows the appropriate transport and storage conditions" [**5].** Analogous information for medicinal products is missing in EC-GMP Guide, Volume 4 Part I [6]. But is provided in the "Guidelines on Good Distribution Practice of Medicinal Products for Human Use" in the paragraphs 20 and 21, which is valid only for finished products but not for bulk drug products [**7].** "Medicinal products should be transported in such a way that their identification is not lost; they do not contaminate, and are not contaminated by, other products or materials; adequate precautions are taken against spillage, breakage or theft; they are secure and not subjected to unacceptable degrees of heat, cold, light, moisture or other adverse influence, nor to attack by microorganisms or pests. Medicinal products requiring controlled temperature storage should also be transported by appropriately specialized means".

The guideline will be replaced by a new guideline which was released for public consultation in March 2013. The requirements on transportation of finished medicinal products are much more detailed as in the current guideline. The following provisions are made in the new guideline in relation to temperature and humidity conditions during transport [8].

- If special storage conditions are required during transport, these should be followed.
- Deviations from defined transport conditions are to be reported to the concerned parties i.e. distributor and recipient and procedures for handling temperature excursions should be established.
- Validation of temperature control systems should be performed for products which require transport at controlled conditions.

- If refrigerated transport vehicles are used temperature mapping should be performed considering seasonal temperature variations.
- If cool packs are used direct contact with the product should be prevented.
- The vehicles used for transport should be suitable for their use. This is the responsibility of the distributor. He has to take care about procedure for operation and maintenance of transport vehicles. When possible, dedicated vehicles should be used for the transport of medicinal products. If non-dedicated vehicles are used, procedures should be in place to ensure that the quality of the medicinal product is not affected by the use of non-dedicated vehicles. The drivers should be adequately trained for transport of medicinal products.
- Temperature monitoring equipment has to be maintained in regular intervals not exceeding one year.
- The residence time at hubs is limited to 24 hours. If 24 hours are exceeded, it is to be regarded as storage.
- Places where unloading and reloading is performed should be audited.

The CHMP guideline "Declaration of Storage Conditions" defines labelling statements which have to be applied depending on the results of stability testing. The labelling statements given in Table 2 have to be used for finished products while the same principles should be applied for drug substances [**9]**. The labelling statements as such are not sufficient to define humidity and temperature ranges for storage areas. For this purpose the temperature definition given in Ph. Eur. General Notices and reproduced in Table 2 can be taken into account [**10].** The current labelling statements are strictly spoken valid for storage only i.e. not for transport with the exception of "Store and transport in refrigerator" and "Store and transport frozen". The labelling statements which indicate storage below 25°C and below 30°C are therefore strictly not applicable during transport. This might make sense for climate zones I and II and for transports which are finished within a short time frame as short time excursions in temperature can be justified under consideration of the MKT but in the light of globalisation with transports through different climatic zones and shipping overseas with transport times of several weeks this seems to be inadequate. In this context transport should be considered as a "mobile form of storage" as stated in the "Concept paper on storage conditions during transport" which targets in closing the gap of clear guidance for storage conditions during transport by a risk based approach [**11].**

Table 2 Storage Conditions, Labelling Statements and Testing Conditions in Europe.

Testing conditions where the product is stable	Required labelling statement	Ph. Eur.
25^0C/60% RH (long term) 40^0C/75% RH (accelerated) or 30^0C/65% RH (long term) 40^0C/75% RH (accelerated)	This medicinal product does not require any special storage conditions	–
25^0C/60% RH (long term) 30^0C/60 or 65% RH (intermediate) or 30^0C/65% RH (long term)	Do not store above 30^0C or Store below 30^0C	–
25^0C/60% RH (long term)	Do not store above 25^0C or Store below 25^0C	Room temperature: 15 – 25^0C
5^0C ± 3^0C (long term)	Store in a refrigerator or Store and transport in a refrigerator	In a refrigerator: 2 – 8^0C
< – 15^0C	Store in a freezer or Store and transport frozen	In a deep freeze: < – 15^0C

USA Guidelines

The General Notices chapter in the USP gives several possible labelling statements which are reproduced in Table 3 [**12].** The labelling statements should be based on stability data. The interpretation of stability data and establishing the labelling statement differs from Europe as a labelling statement is also required if stability data at accelerated conditions (e.g. 40°C/75% RH) are available. Data gained at accelerated

storage conditions might be taken into consideration for interpretation of transient temperature spikes which exceed the temperature excursion range of controlled room temperature.

Table 3 Storage Conditions and Labelling Statements According to USP (12)

Labelling statements	Storage conditions
Freezer	– 25^0C to – 10^0C
Refrigerator	Usually 2 to 8^0C. Excursions between 0 – 15^0C are acceptable if the MKT is less than 8^0C Short term spikes of up to 25^0C for maximum 24 hours are allowed if permitted by the manufacturer. For excursions exceeding 24 hours, transient spikes have to be supported by stability data
Cool place	8 to 15^0C
Controlled room temperature	Usually 20 – 25^0C. Excursions between 15 – 30^0C are acceptable if the MKT is less than 25^0C Short term spikes of up to 40^0C not exceeding 24 hours are allowed if permitted by the manufacturer. Short term spikes of more than 40^0C have to be supported by stability data

The USP monograph <1079> "Good Storage and Shipping Practice" gives requirements for storage, distribution and shipping of medicinal products. Concerning transport of medicinal products the following provisions are made:

During transportation as a general rule extreme temperature conditions such as excessive heat or freezing should be avoided. Temperature measuring devices which are used have to be calibrated.

Shipping vehicles for articles which require controlled room temperature storage are to be equipped in a manner which ensures that the temperature excursions in the range of 15°C to 30°C with a MKT not exceeding 25°C. The vehicles should be qualified considering the load configurations and expected environmental extremes. Qualification should include temperature mapping over a 24 hours period on a hot summer day, a typical day and a cold winter day. In order to evaluate the influence of multiple short-term excursions, temperature cycling studies should be performed for products which require special storage conditions. Temperature cycling studies mean stability studies where sequential cycling between lower and higher temperatures is performed. For products requiring cold chain management temperature mapping has to be performed [**12**].

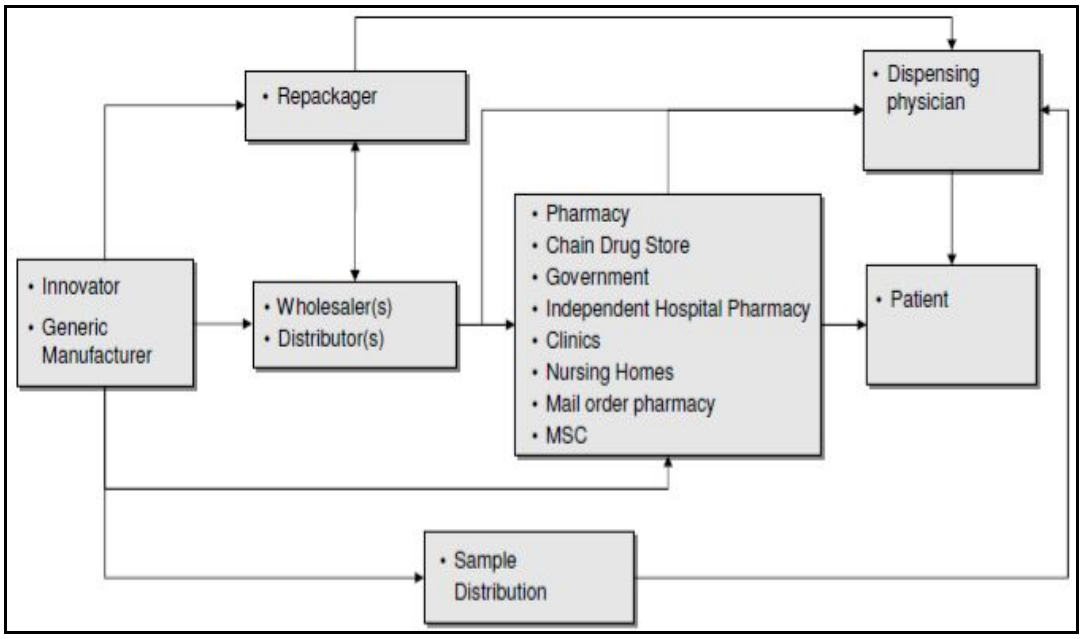

Figure 1 illustrates the scheme of drug distribution in USA.

ICH Guidelines

In the Q5 guideline, under "Storage Conditions Part 6.3, Accelerated and Stress Conditions 10" the ICH recommends that stress tests be performed in order to define the conditions that may occur during transportation and which will affect the product. To recommend testing, the guide is necessarily broad because of all the different types of products that might be shipped. The testing will not only determine the conditions that impact the product, but should also determine which tests are best for determining stability.

"Studies under stress conditions may be useful in determining whether accidental exposures to conditions other than those proposed (e.g., during transportation) are deleterious to the product and also for evaluating which specific test parameters may be the best indicators of product stability. Studies of the exposure of the drug substance or drug product to extreme conditions may help to reveal patterns of degradation; if so, such changes should be monitored under proposed storage conditions. And that the conditions should be carefully selected on a case-by-case basis.[13]. Likewise for new drug substances and products: "Data from the accelerated storage condition and, if appropriate, from the intermediate storage condition can be used to evaluate the effect of short term excursions outside the label storage conditions (such as might occur during shipping) [14].

ASEAN Guidelines

There are no well defined ASEAN guidelines for storage and transportation of pharmaceuticals or drug products. In principle, it is assumed that countries covered under ASEAN have to adopt WHO guidelines for drug product storage and transportation.

The goal of any supply chain is to transport products from the manufacturer to the consumer. However, the success of a supply chain depends on and is measured by its ability to deliver products that can serve their ultimate purpose with the end user. In pharmaceutical supply chains, this means that a product must arrive unadulterated and with its efficacy fully intact. In the context of a successful supply chain, organizations that enforce regulations and create quality standards act not only as arbiters, but as partners in quality. With globalization and emerging markets, many countries look to ICH and the USFDA for guidance in approaches to improving supply chain control and performance. It follows that basing your regulatory compliance firmly in the regulations, standards and guidelines of these two organizations will ensure that the fundamental requirements of a safe supply chain for drug products.

Regulatory provisions in India

In India the sale, purchase, distribution and import of drugs and cosmetics is regulated by Drugs and Cosmetics Act 1940 and Rules 1945. Provisions for Good Manufacturing Practices are covered under Schedule M of the Act, which states conditions for warehousing of pharmaceutical products –

- Adequate areas shall be designed to allow sufficient and orderly warehousing of various categories of materials and products like starting and packaging materials, intermediates, bulk and finished products, products in quarantine, released, rejected, returned or recalled, machine and equipment spare parts and change items.
- Warehousing areas shall be designed and adapted to ensure good storage conditions. They shall be clean, dry and maintained with acceptable temperature limits, where special storage conditions are required (e.g. temperature, humidity), these shall be provided, monitored and recorded. Storage areas shall have appropriate house-keeping and rodent, pests and vermin control procedures and records maintained. Proper racks, bins and platforms shall be provided for the storage of materials.
- Receiving and dispatch bays shall protect materials and products from adverse weather conditions

However, the Schedule M does not mention about the conditions to be followed during transportation of pharmaceuticals and onus of product safety and stability lies on the manufacturer.

The Central Drugs Standard Control Organization (CDSCO), the national regulatory body governing pharmaceuticals and medical devices in India, issued draft guidelines in January 2013, designed to ensure the quality and identity of pharmaceutical products throughout the distribution process.

The draft CDSCO Regulations cover a broad range of issues and activities that are intrinsic to a validated supply chain:

- Appropriate organization and management of suppliers
- Personnel and training
- Quality systems and self-inspection in keeping with ISO or other accepted national or international guidelines
- Warehousing and storage
- Temperature control of both products and the storage environment
- Inventory control
- Transportation
- Dispatch and receipt of goods
- Documentation and record-keeping
- Complaint mechanisms
- Recalls and returns
- Counterfeit pharmaceutical products
- Importation
- Contractual obligations

While the introduction of GDP guidelines has generally been applauded, the implementation of these regulations and the inspection and verification of suppliers, processes and product is seen as a challenge. Similarly, upgrading the in-country storage infrastructure to an acceptable level to accommodate cold chain requirements and mandatory compliance of GDP may be a lengthier process that needs to be phased in.

The manner in which WHO, EU, US FDA and other regulatory agencies have clearly defined the conditions for storage, distribution and warehousing of pharmaceuticals is not reflected in the draft guidance prepared by CDSCO. Considering the vast geographical and climatic variations in our country and manner in which pharmaceuticals are transported and stored, monitoring the changes in temperature and/or humidity that occur during transit and evaluating its impact on product potency/stability is essential.

The present study proposes recommendations with the objective of aligning India with the more advance drug regulatory agencies in addressing the issues of pan India storage and transportation of Pharmaceuticals.

Recommendations

In general context, following factors are critical when working to minimize variability of storage, handling and distribution on pharmaceutical product quality, safety and stability –

Customs/octroi and stoppages during traffic jams - Pharmaceutical products do get held up during inspection at customs or at octroi posts during interstate transits. They may also get stranded during traffic jams or delays may happen for some reason during road/surface transit. Delays of up to four weeks in shipping to distant places within the country have been experienced.

Hemispheric, climatic and seasonal variations – The time of year shipments are made is critical. Products that are shipped internationally often travel through different hemispheres and climates. For instance, it is highly possible that a pharmaceutical may originally ship out of the warm climate of India, have the product repackaged in the winter frigid weather of Canada, yet end up in the tropical heat of Florida—all within a week's time (that is, if there are no delays at customs). Thus, the shipment will be exposed to warm and possibly freezing temperatures before it gets to its final hot-weather destination. The product, packaging, and shipments all will need to effectively manage extreme temperature variation. Similarly, in most cases, interstate transportation of pharmaceuticals will result in the drug product being exposed to drastic variations in climatic conditions. Furthermore, if the pharmaceuticals are transported in an outermost steel container, an external weather condition of 40^0C can in fact result in a rise in temperature to beyond 50^0C inside the container. Hence, it becomes imperative that the steel vans transporting the drug products are insulated to prevent extreme fluctuations in temperature owing to exposure to outside atmospheric conditions.

Modes of transport – When transporting shipments via van and truck —between distribution centres or to and from the airport — it is important to know what specific temperatures will be experienced. For instance, if shipping from a cold winter climate, such as Canada, temperatures can dip down to –20°C. These

same freezing temperatures could be experienced on the back of the truck. If temperatures on the back of the truck are expected to be this extreme, it may be best to transport the pharmaceutical products with a heated trailer, instead of a refrigerated trailer. Vice versa is possible in tropical countries like India and hence the need to address the material of construction of vans that are used to transport the drug products.

The system for monitoring a drug's temperature throughout the supply chain is not only highly complex, but also highly variable. The distribution environment depends on a range of factors, such as points of origin and destination, article and container sensitivities to cold and heat, accidental freezing, transit mode (e.g. air, truck, ship or a combination), trade lanes, time, weather, season, carrier type (e.g., small and large package providers), etc.

Need to Define 'Distribution Temperature Profile' (DTP)

The distribution temperature profile table is created utilizing stability data that outlines shipping time and temperature conditions that a drug product may be exposed to, that still ensure minimal risk to a drug product's chemical (potency) and physical properties.

- Finished product must be shipped in accordance with local regulatory requirements.
- Acceptable temperature range (shipment conditions) may be appropriate within which a drug product can be transported for a defined duration of time without adverse effect on its quality.
- This must be supported by stability studies/product temperature excursion studies.
- Stability data is required to determine temperature and time limitation requirements for finished product shipments.

An example of proposed excursions for cold chain products during transportation is presented in table 4.

Table 4 Refrigerated Drug Products – Storage and Excursions.

	Allowable exposure temperature range	**Allowable exposure time**
Recommended storage	2 to 8^0C	Until expiry date
	< 0^0C	Should be avoided
Shipping and distribution exposure conditions	0 to 1^0C	24 hours
	2 to 8^0C	Until expiry date
	9 to 20^0C	6 days
	21 to 25^0C	3 days
	26 to 30^0C	36 hours
	31 to 40^0C	8 hours
	> 41^0C	Should be avoided

An example of proposed excursions for products intended to be stored at room temperature during transportation is presented in Table 5.

Table 5 Refrigerated Drug Products – Storage and Excursions

Item	**Avoid**	**2 days**	**Distri-bution time**	**Until expiry**	**6 days**	**4 days**	**3 days**	**2 days**	**24 hours**	**4 hours**	**Avoid**
A	< -20^0C	-20 to 1^0C	2 to 14^0C	15 to 30^0C				31 to 40^0C	41 to 60^0C		≥ 61^0C
B	< -20^0C	-20 to 1^0C	2 to 14^0C	15 to 30^0C	31 to 40^0C				41 to 60^0C	61 to 70^0C	≥ 71^0C
C	< -20^0C	-20 to 1^0C	2 to 14^0C	15 to 30^0C			26 to 50^0C				> 50^0C
D	< -20^0C	-20 to 1^0C	2 to 14^0C	15 to 30^0C		26 to 40^0C		41 to 50^0C			> 51^0C

Examples of proposed excursions for products that require storage at or below 25^0C and 30^0C, during transportation and/or warehousing are presented in Table 6 and 7.

Table 6 Product having Storage Condition at or below 25^0C – Proposed Excursions.

	Allowable exposure temperature range	**Allowable exposure time**
Recommended storage	2 to 8^0C	Until expiry date
	< 0^0C	Should be avoided
Shipping and distribution exposure conditions	0 to 1^0C	24 hours
	2 to 8^0C	Until expiry date
	9 to 20^0C	6 days
	21 to 25^0C	3 days
	26 to 30^0C	36 hours
	31 to 40^0C	8 hours
	> 41^0C	Should be avoided

Table 7 Product having Storage Condition at or below 30^0C – Proposed Excursions

	Allowable exposure temperature range	**Allowable exposure time**
Recommended storage	2 to 8^0C	Until expiry date
	< 0^0C	Should be avoided
Shipping and distribution exposure conditions	0 to 1^0C	24 hours
	2 to 8^0C	Until expiry date
	9 to 20^0C	6 days
	21 to 25^0C	3 days
	26 to 30^0C	36 hours
	31 to 40^0C	8 hours
	> 41^0C	Should be avoided

Scientific/Risk Management Approach

The figure below illustrates the risk management approach to address issues arising out of pharmaceutical distribution. Figure below illustrates the risk management approach to address issues arising out of pharmaceutical distribution.

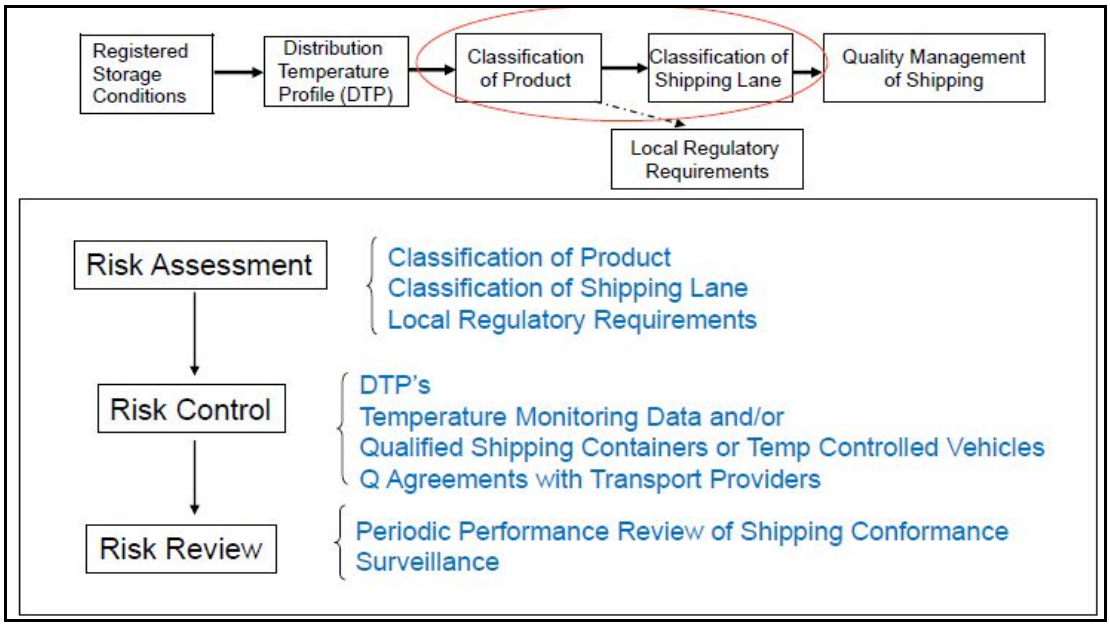

Figure 2 Figure below illustrates the risk management approach to address issues arising out of pharmaceutical distribution.

Dr. Mashelkar committee's recommendations [15] were grossly stated but in-depth analysis and clear definition of procedures, guidelines and statutory requirements need to be framed to account for safety and efficacy of drug products as a result of distribution and warehousing. The significant and crucial role of the distribution channels of drugs and pharmaceuticals (wholesale as well as retail) cannot be over-emphasized. It is important to note that medicines take a long winding and circuitous route before they reach the consumers. Figure 3 illustrates the drug distribution chain from India's perspective.

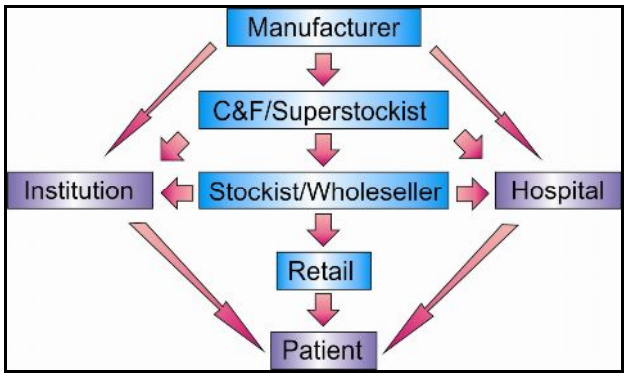

Figure 3 Drug distribution chain in India.

Trade and professional associations, Pharmacy Council of India as well as State Pharmacy Councils need to play a much larger role to reform the drug management and patient interface practices in retail outlets. It is not tenable to enforce professionalism through one or two annual inspections by drugs inspectors. In this regard, the Committee noted that the Government has made a very clear policy statement in the preamble of Pharmacy Act 1948 which states "it is expedient to make better provisions for the regulation of the profession and practice of pharmacy and for that purpose to constitute Pharmacy Councils". There is an urgent need to implement India specific Good Pharmacy Practices and Good Storage and Distribution Practices that will minimize the chances of poor quality medicines reaching the end user. Pharmacy Councils must perform a proactive role in bringing awareness about these concepts and should ensure that their knowledge is linked with the registration under the Pharmacy Act. It must be emphasized that in several countries the responsibility of regulating retail sale of drugs is entrusted with professional bodies or state boards that register pharmacists. Continuing education for renewal of registration as pharmacists is also mandatory in several countries. In India, the registration of pharmacists, under the Pharmacy Act is done by the State Pharmacy Councils while the licensing of retail outlets where these pharmacists are deployed, is done by the Drugs Control Department under the Drugs & Cosmetics Act and Rules. There is a need to review this system and possibly integrate pharmacists and the pharmacy profession and make them more accountable for their roles in drug distribution. The concept of locum (stand-in or substitute) pharmacists may be introduced to further ensure that the drugs in supply chain are managed in an appropriate manner, till they reach the patients.

Guidance documents issued by several other countries and governmental agencies including WHO, illustrates that regulatory requirements for storage, distribution, shipping and warehousing of temperature-sensitive pharmaceuticals continue to expand globally. As expectations for compliance have increased, so have responsibility and liability issues, which no longer end with the drug manufacturer. Strict adherence to regulatory requirements has placed increased importance on qualified packaging, qualified distribution systems and compliant storage practices.

- Qualifying packaging for the transport of temperature-sensitive products provides a high level of assurance that product integrity has not been compromised owing to hazards within the distribution environment and that regulatory requirements have been met.
- Qualified packaging maximizes efficiencies in package design and may help reduce overall shipping expense by minimizing material cost, storage space, and package weight, thereby reducing freight charges.
- Understanding the distribution chain is key to qualifying a properly engineered package.
- Creating temperature profiles that realistically reflect those found within a given distribution system requires a thorough understanding of perennial Indian climatic conditions.

- Monitoring the distribution chain for changes in temperature as a result of environmental change and handling practices is an ongoing necessity in order to establish trends, capture emerging modes and set realistic limits.
- A key element that must be considered when developing a temperature test profile must include accepting a percentage of risk of exposure to extremes in temperature and determining a confidence interval associated with that risk.
- The Schoenherr Model of Profile Development for temperatures in distribution is a practical, statistically relevant, accurate and repeatable process for developing a temperature profile based on a specific distribution environment [16] (Distribution processes should be monitored to determine trends and identify factors that influence changes to the system. Ongoing monitoring programs also provide supporting documentation for continuous improvement for temperature-sensitive drug distribution.

A brief temperature exposure profile of a product manufactured at Sikkim when distributed to Chennai over a period of 15 days, will be exposed to following variations in temperature and/or humidity during its transit (transport commencing May 1st). The same is graphically represented in Figure 4.

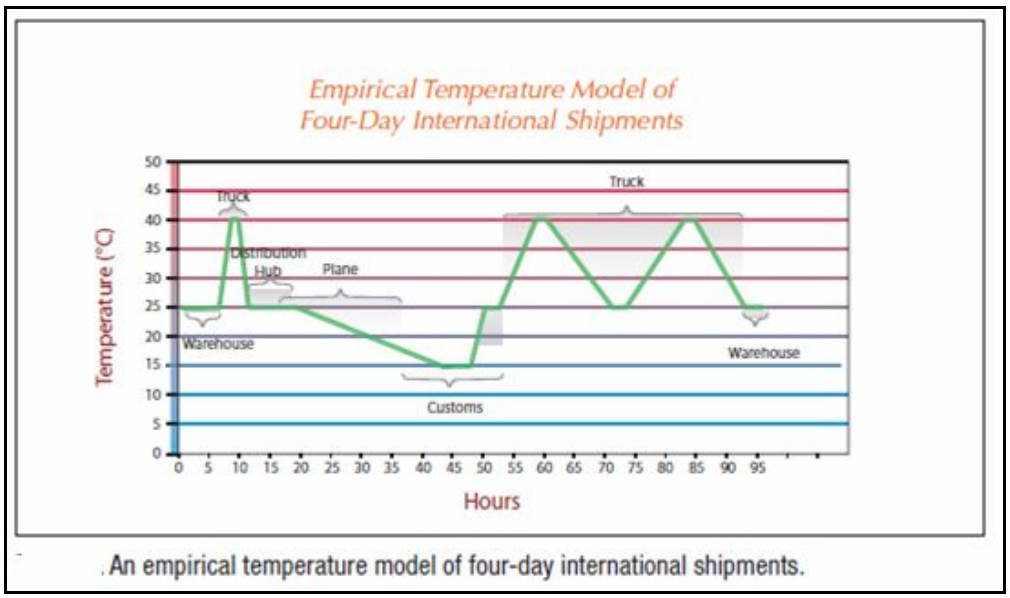

Figure no 4 illustrate an empirical temperature model of four –day international shipment.

Drugs can be sensitive to environmental conditions such as temperature, humidity, light, oxygen, shock, pressure, vibrations, and X-rays. Drug degradation depends on the value of the environmental conditions and the period of time during which the product is kept at this value. Claude Amsann's [17] recommendations for conditions to be tested for transport of various drug products are presented in Table 8.

Table 8 Example of Conditions to be tested for Product Transport.

Example of Conditions to be Tested for Product Transport

	Temperature	Humidity	Light	Pressure	Vibrations	Shocks	X-ray
Solid in bottles	+	0	–	–	0	0	–
Solid in blisters	+	0	–	+	0	0	–
Liquid in ampoules	+	–	–	–	0	+	0
Liquid in bottles	+	–	–	–	0	+	0
Liquid in sprays	+	0	–	+	0	–	0
Gel in plastic tubes	+	–	–	0	0	–	0
Cream in plastic tubes	+	–	–	0	0	–	0

(–) conditions not requiring tests, *0* conditions possibly requiring tests, (+) conditions definitely requiring tests

Temperature is the main focus for testing because almost all pharmaceutical and biotechnological products are sensitive to temperature. In addition, transport in controlled conditions is not always reliable. There are a number of problems that can arise:

- Weather might follow unpredictable changes
- Customs/octroi procedures might take longer than anticipated
- Accidents might cause disruption
- Route used for transport might not be that anticipated
- Transport might stop at unsuitable places
- Temperature control systems might malfunction
- Communications between the various transport companies might have blocked the product (this could happen when the transport is contracted out to a chain of transport specialist such as shipper, forwarders, ground handlers/transportation service providers, consignee, air carrier)
- Temperature sensors might be defective
- Information on the actual transport conditions might not be exact or may be lacking
- Other factors.

For these reasons, the manufacturer should make the best possible efforts to obtain formulation that is "stable" under a broad range of conditions. If this is not possible, the next objective should be to assess extensively the limits in which the product can be handled safely. There are natural temperature ranges that could be defined. In Ladakh, temperature minima have been measured at −40°C. Temperature maxima have been measured at +50°C in Rajasthan. But even if a product is stored in a closed environment under the sun, it will not be heated over 100°C.

Humidity during transport is generally not critical due to the very short period of time when the product is stored at high/low humidity. But humidity can change the characteristics of solids or non-aqueous solutions which are packed in non-tight containers. Preservation of a drug product at high or low humidity is a testing condition of the ICH/WHO studies, and it is usually not necessary to repeat/add this parameter to the transport/distribution stability program.

Different types of studies are suitable for defining product's sensitivity to distribution.

- Temperature excursion studies and cycling studies [18]
- Freeze-thaw studies are another type of study that can be valuable for biologics or biotechnological products since their structure might be changed by freezing/thawing conditions. Presence of particles has also been observed after such temperature variations.
- Real time studies such as those performed with a temperature program simulating the real transport conditions e.g., during summer and winter times are best suited when the manufacturer knows quite accurately what the distribution channels are.

Conclusion

The manufacturer must ensure that products delivered to patients comply with the marketing authorization. For products sensitive to transport conditions, this means that the manufacturer has to control the product stability profile and choose the correct storage conditions and appropriate transport systems. When the transport conditions deviate from the specified values, there is a sound basis to decide whether to release or to reject the batches.

The storage conditions are best determined in accordance with the well established country-specific or ICH/WHO stability testing programs. Transport conditions have to be determined considering the risks of product degradation. If the product is very sensitive to one or more parameters, the manufacturer has little margin to set the transport conditions. Tight limits, identical or close to those of the storage conditions, will be required. On the other hand, if the product is somewhat resistant to extended parameters for a short period of time, it is in the interest of the manufacturer and the users to have extended transport conditions. In the example of a refrigerated product, the chosen transport conditions could be "room temperature" or "controlled room temperature", allowing the product to be transported in conditions that are not too difficult to guarantee for the

many transport operations that are necessary to reach the patients. The risks of deviations are diminished, without increasing the risk to the patients.

The preliminary information needed to optimize transport conditions is knowledge about product sensitivity to the relevant transport parameters. Tests in addition to those proposed by the ICH/WHO guidelines should be planned to complete the picture.

Conflict of Interest

Author declares no conflict of interest.

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