HEC MONTRÉAL

Selection of Cold Chain Packaging Solution Using an Interpretive Structural Modeling (ISM) approach

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ABSTRACT

In a ‘cold chain’, the quality of service is heavily dependent on the investment in modern technology and equipment, especially on cold chain packaging solution. Companies who never faced temperature excursion on their drug shipments still continue to use expensive active packaging containers and ignore the chances that their packaging may be over-engineered than required. But this over-engineering comes at an additional price that increases the overall cost of their shipment (Kohleriter, 2013). Due to the tough economic times and highly competitive market these days, many pharmaceutical companies are becoming more cost conscious and are looking for different ways to minimize cost. There are thoughts about reducing the cost by using cheaper packaging solutions such as passive packaging system, but this comes at the risk of exposing the products to the ambient temperature. These minor cost saving might be attractive in the short term but all those savings can be wiped out if a single shipment faces a critical temperature excursion before it reaches the final user (Grubb, 2013). Therefore when it comes to distributing these temperature sensitive drugs, pharmaceutical companies should try their best to use the most ideal packaging solution that fits their particular situation.

In this thesis, we approached some key industry experts to understand the key factors involved in taking a cold chain packaging decision. We extended our study by performing a detailed investigation about the factors by using a methodology known as Interpretive Structural Modeling (ISM). Many researchers have used this methodology to understand the interrelation between various elements. We will conclude our study by generating an flow chart diagram that portrays a decision-making process level by level. We expect that the result from this diagram will be beneficial to the various cold chain players in making wiser packaging decisions.

Keywords: Cold chain, packaging system, interpretive structural modeling, temperature sensitive, pharmaceutical drugs, biologics, goods distribution practice (GDP)

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

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1. INTRODUCTION

1.1 Research problem

Cool Chain Association (CCA) estimates that 30% of the temperature-sensitive products are mainly lost during the transportation process (Hoffman, 2006). One of the major reasons for such wastage is the result of poor 'cold chain' controls, which includes lack of proper planning and coordination (Prakash, Renold, & Venkatalakshmi, 2012) in spite of best intention by the drug manufacturers and the logistics providers (East, Smale, & Kang, 2009).

By the time a temperature-sensitive product reaches the hands of the end user, it would have transited through several actors in the supply chain using several storage and cold chain equipment (Sahin, Babaï, Dallery, & Vaillant, 2007) and facilities. This has created a web of uncertainties and interdependencies (Goetschalckx, Vidal, & Dogan, 2002). In spite of many technical and managerial solutions available today to maintain a controlled temperature distribution, there is no ideal solution or methodology that exists to achieve good results (Montanari, 2008).

1.2 Purpose and objective of the study

In cold chain, the quality of service is heavily dependent on the investment in modern technologies and equipment. Cold chain technologies and equipment includes different types of refrigerated containers, different data loggers for the purpose of temperature monitoring, time temperature integrators (TTI) for managing product's life period, and cold chain packaging solutions. Several studies has been dedicated to various areas of the cold chain such as use of time-temperature integrators, temperature monitoring devices, cold chain networks, coping with regulations pertaining to the distribution of these temperature controlled products etc. But very little attention has been given to the area of cold chain packaging solution, which is an important cold chain equipment that can help to minimize the wastage that occurs during the transportation process.

Therefore, the objective of our study is to identify the various decisive factors involved in making a cold chain packaging decision, then perform an investigation about their individual characteristics, their significance and the interrelations between them. Finally, we will develop a framework using an ISM methodology to help the cold chain managers make wiser cold chain packaging decisions.

Since packaging is only a small sub-section of the cold chain, it is important that the reader has some basic knowledge about the other areas of the cold chain. So a general introduction about the various aspects of the cold chain is presented in the literature review section.

1.3 Research question (s)

a) What are the most important decisive factors in selecting a cold chain packaging system for biologics drugs?
b) What are the most and least influential factors among them? What are their significance and inter-relation between these factors? How can managers use them to make better cold chain packaging decisions?

The remainder of this thesis is organized as follows: Section 2 is a literature review that gives a general insight into the various aspects of the pharmaceutical supply chain, especially the cold chain. Section 3 explains the research methodology. Section 4 will describe the application of the proposed methodology, data collection process and compilation of the data. Section 5 shows the results generated by the proposed methodology, followed by analysis and discussion. Section 6 will have our conclusion. Section 7 will discuss the limitation of our research and future research opportunities.

2. LITERATURE REVIEW

The literature review section gives an introduction about the different areas of the cold chain. It covers topics about the different cold chain products, regulatory guidelines, key players in the cold chain, various transportation modes, problematic areas, and cold chain equipments and technologies, etc. This study will be focused on the transportation of biologics drugs. The nature, characteristics, risk and importance of this cold chain product are explained in the following paragraph.

2.1 - BIOLOGICS

Biologics are technically a subset of bio-pharmaceuticals drugs. (Wikipedia, 2013). The difference between biologics drug and normal chemical drug is that biological drugs have pinpoint accuracy in searching for the diseased organs or cells that needs to be treated. These are the drugs of the future and they are developed through advanced technology called "genetic modification" (T. Nelson, 2008). These are a new class of complex protein-based therapeutics that is produced by manipulation of living organisms to cure, treat or prevent disease. This makes it very different from conventional small-molecule drugs (Revers & Furczon, 2010). Common examples of biologics are vaccines, insulin, human growth hormone, HIV/AIDS medication, blood components, monoclonal antibodies (MAbs), etc.

Importance of biologics drugs

Biologics drugs are high revenue-generating asset for licensed companies. Developing, manufacturing and commercializing biologics are not only scientifically complex, but it is also very expensive, time-consuming and highly regulated. "*The average time needed to develop a biological drug can vary from 10 to 15 years and the average investment into research and development can cost $1.2 billion" (BlackStone, 2012).* Yet the success rate of the drug candidates after completion of the drug's clinical trial is only about 1 in 10 (Young, 2010). Development of pharmaceutical product is characterized by its high sunk cost, high risk and long payback time. This is the reason why the average selling price

of drug can be many times higher than its actual cost of ingredients, as they have a very short time window to set a monopoly price (Pedroso & Nakano, 2009).

Environment risk of biologics products

"The drugs comprise long protein strands and are by nature sensitive to changes in temperature, especially when exposed to frozen temperatures and extreme heat. Their instability to temperature changes can break the protein bonds and denature the drug, resulting in compromised quality that can directly affect the efficacy of the drug and may affect its purity, potency and potential safety to the patient. Some biologics are also sensitive to light and certain frequencies of vibration. Temperature assurance is critical during the storage, packaging, transportation, and delivery of biologic drugs within the distribution system – from manufacture to patient use" (O'Donnell, 2011, p. 7).

In the case of vaccines, once the potency has been lost through exposure to excess heat or cold, it cannot regain its quality even if it is put at the correct storage temperature. As they do not change their appearance due to damage, it is impossible to even see the difference without conducting a laboratory test (Chatterjee & Pandey, 2003). On the contrary, keeping vaccines under extreme cold can be just as harmful as keeping them too warm because many vaccines can also get damaged due to freezing (WHO, 2007). Several epidemiological studies have proved that freezing of vaccine is a possible contributor for the low immune response of these drugs in the vaccinated individual (Matthias, Robertson, Garrison, Newland, & Nelson, 2007). In the case of transportation of red blood cells (RBCs), failure to refrigerate adequately can result in transfusion of that blood which can directly reduce not only the therapeutically effectiveness, but also a potential for increased mortality (Sharley, Williams, & Hague, 2003).

Current growth potential and rising demand

The healthcare sector projects that 50% of all new drug approvals in the US will be biologics by 2015 (S. Moorkoth, 2013). Since many existing patents are beginning to expire, this will open the gate for production of biosimilar by generics houses.

Also according to a report from Scientia Advisors, worldwide sales of vaccines are predicted to rise from $16 billion in 2007 to $35 billion in 2014 (Roth, 2009). This number shows its huge growth potential in the coming years. Large pharmaceutical companies clearly understand the pressure of getting their new products to the market on time. For example, Canadian law grants 20 years of patent protection to companies that develop new drug. This is a window time designed to allow developers of breakthrough medicines to see a fair commercial return on their investment. Yet many pharma players lose more than half of that time window due to complex regulation, human resource issues, supply chain problems, and other jams along the product pipeline. These companies in turn face their own challenges, which include marketing and distribution (PwC, 2014). Table 1 shows some of the top bio-pharmaceutical companies in Canada:

Table 1 - Leading Pharmaceutical Companies in Canada

Leading Pharmaceutical Companies in Canada

Rank	Companies	R&D Location in Canada	Total Sales ($ Billions)	Market Share (%)
1	Pfizer	Montreal	2.94	13.4
2	Apotex	Toronto	1.55	7.0
3	AstraZeneca	Montreal	1.44	6.6
4	Schering-Plough	Montreal	1.33	6.0
5	Johnson & Johnson	Toronto	1.16	5.3
6	Novopharm	Toronto	0.92	4.2
7	Novartis	Toronto	0.89	4.0
8	GlaxoSmithKline	Toronto	0.88	4.0
9	Abbott	Montreal	0.85	3.9
10	Roche	Montreal	0.68	3.1

Source : Industry Canada (2009).

Source: (Abscisse, 2011)

2.2 – COLD CHAIN

In the supply chain context, “a chain is defined as the process of linking suppliers and users, from the initial raw materials to the ultimate consumption for the finished product” (Omta, Trienekens, & Beers, 2001, p. 2). A ‘cold chain’ is a temperature, humidity, and light-controlled supply chain for products that require a specific temperature range during distribution and storage. The transportation phase (which also includes loading, unloading, handling and storage) plays a

dominant role in maintaining the desired temperature requirement of the drug (Montanari, 2008) and also to preserve the value to the end customer (Salin & Nayga Jr, 2003).

There are several types of products that require temperature-controlled supply chain such as fresh agricultural produce, frozen food, chemicals, pharmaceutical drugs (Prakash et al., 2012), flowers, semi-conductors (Salin & Nayga Jr, 2003). However, the biggest growth in cold chain comes from the healthcare industry (O'Donnell, 2011). *Table 2* shows the different temperature requirement for each category of products.

Table 2 - The Various International Temperature Requirements

Category	International Storage and shipping requirements (stated in Celsius and Fahrenheit)
Frozen	- 25° and -10° C (-13 and 14° F)
Cold	Any temperature not exceeding 8° C (46°F)
Cool	Between 8° and 15° C (46° and 59° F)
Temperature controlled	Thermostatically controlled temperature of 20° to 25° C (68° to 77° F)
Room temperature	Temperature prevailing in a working area; not thermostatically controlled
Warm	Between 30° and 40° C (86° and 104° F)
Excessive heat	Above 40° C (104° F)

Source: (Reed, 2012b)

Drug Distribution Problem

The combination of the rapid globalization of the pharmaceuticals market and growing demand for biologics is making the transportation of healthcare products an increasingly complicated challenge for pharma companies. Environment factors are a huge risk when it comes to cold chain management. For example, in regions like Africa, China and India, the temperature and weather can vary even within the

same country (WorldPharma, 2013). Environmental concerns (risks) such as inadequate temperature (extreme weather), humidity, light and vibration can all directly affect the drug's efficacy, potency, purity and quality (O'Donnell, 2011).

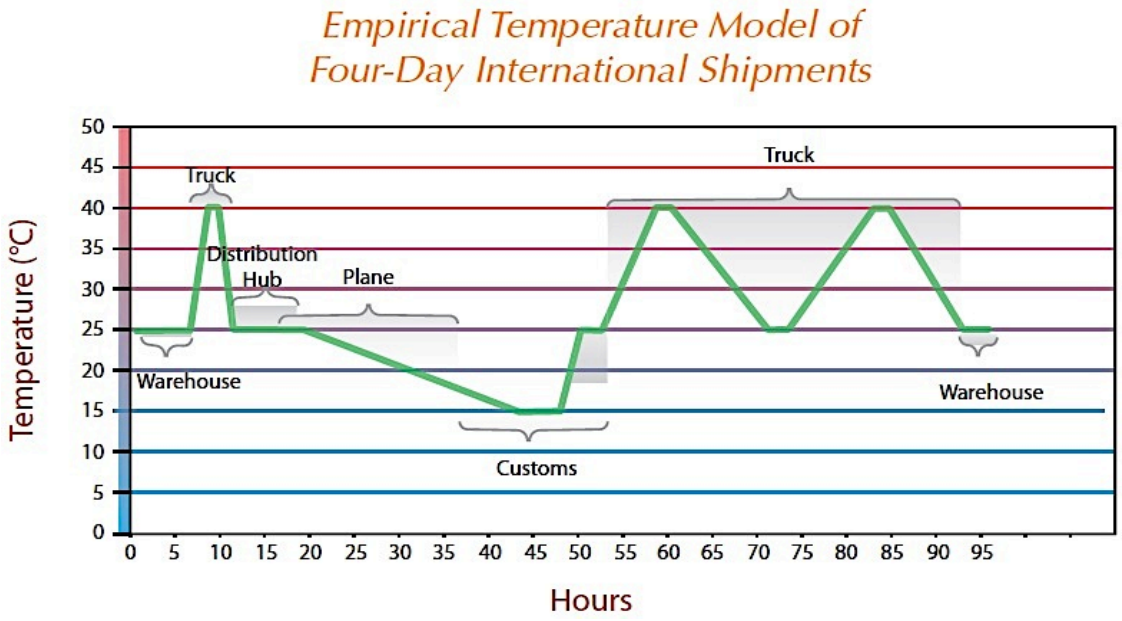
It has been assumed that the logistical difficulties of biologics drug distribution in an industrialized country would be minimal. However, it appears that serious logistical failure can also take place in developed countries with extreme temperate climate (extreme winter & summer temperate). Therefore it is necessary to ensure that proper cold chain controls are in place in-order to protect these drugs (Lugosi & Battersby, 1990). In spite of many technical and managerial solutions available today to maintain a controlled temperature, there is no ideal methodology that exist to achieve the ultimate solution (Montanari, 2008). Lack of understanding of the cold chain procedures appear to be a main contributor to this problem (C. Nelson et al., 2007).

WHO recommends that all vaccines must be kept at a temperature between 2-8 degree Celsius during their distribution (WHO, 2007). Since most cold chain practices mainly emphasize on protection of vaccines from heat damage, there has been several situations where vaccines have faced the risk of exposure to freezing temperature (Matthias et al., 2007). The most common place where the risk of freezing occurs is during the transportation (Wirkas, Toikilik, Miller, Morgan, & Clements, 2007). During transportation, these vaccines face risk because they are placed close to frozen ice packs inside insulated carriers. So WHO started giving specific guidelines by recommending to use of 'conditioning ice packs'. This can be done by allowing the 'ice packs' to begin their melting stage before placing them in the insulated box (Matthias et al., 2007; C. Nelson et al., 2007).

When the target markets are located in a developing country where there is a logistics constraint, it can be more challenging to maintain the functioning of these chains. The two key stressing points in the cold chain in developing countries are a) unavailability of quality cold storage capacity outside of the capital city; and b) high cost of distribution (Salin & Nayga Jr, 2003).

An example of international season variation will be a pharmaceutical drug originally shipped out of the warm climate of India, which will have to be repackaged in the winter climate of Canada, and finally end up in the tropical climate of Florida in a week's time. Such shipments need to take consideration of the extreme temperature variation (Bishara & O'Donnell, 2007). Figure 1 supplements our explanation.

Figure 1 - Empirical Temperature Variance in an International Shipment



Source: (Bishara & O'Donnell, 2007)

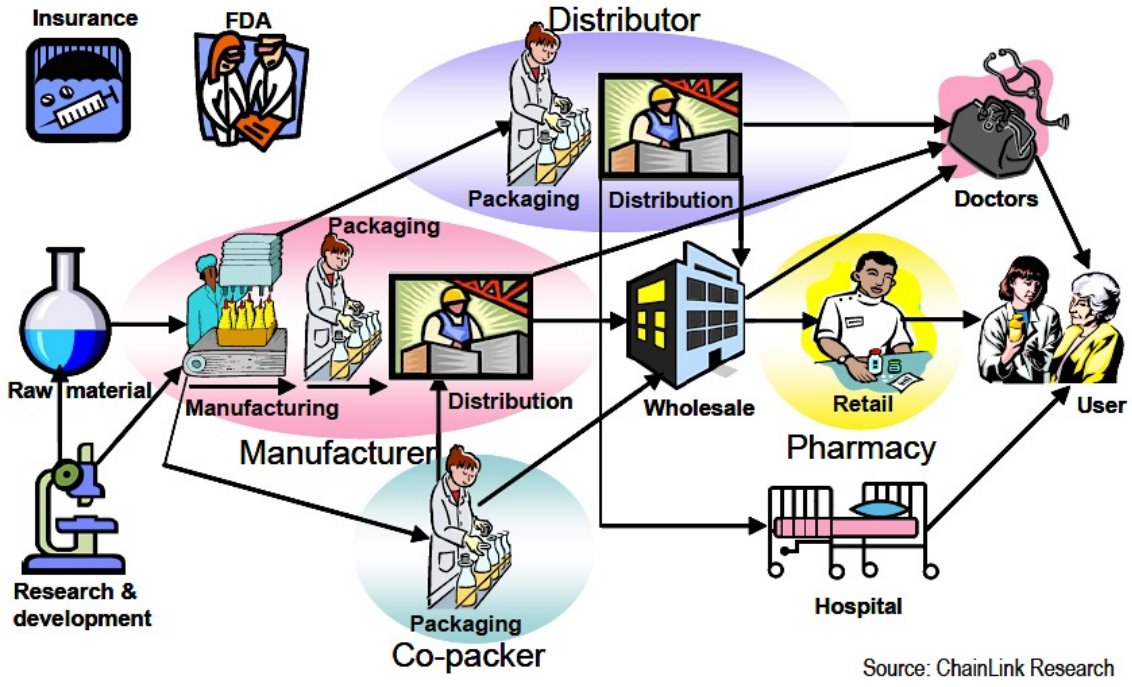
There has been a low quantum of trans-continental research covering Asian and African regions where logistics infrastructure is weak or different (Narayana, Kumar Pati, & Vrat, 2014). Geographic considerations, language barrier, customs clearance procedures all can affect distribution and logistics models. Therefore, a planned distribution model has to be designed for shipments to these developing countries. Due to their high value and low tolerance to environmental risks, biological drugs are most often transported by the fastest & safest way possible, thus making it the highest value-per-kilo cargo, both in terms of money and intrinsic value (AACargo, 2010).

The recent investment of US$1.4 million by the Bill & Melinda Gates Foundation towards innovative refrigeration technology to bring a life-saving vaccine cooler to final consumer is an important development (Dahad, 2014). Several other grants have also been made by the same donor in the previous year worth $1,797,275 and $998,287 (Fondation, 2013; Foundation, 2013). The aim was to develop a new class of passive cold chain equipment to prevent the freezing of vaccines and to ensure the safe delivery of these drugs. All these are indicators of an existing problem and the needs for a better logistics solution.

2.3 – KEY PLAYERS IN THE COLD CHAIN

The pharmaceutical supply chain is very different from the supply chain of other industries (Fein, 1998; Danese, Romano, & Vinelli, 2006). Literature indicates that pharmaceutical industry has one of the most fragmented supply chain (Narayana et al., 2014). Cold chain being a sub-set of this pharmaceutical supply chain makes it very complicated. The integrity of the cold chain has to be preserved from the point of production, through each of the transport phases which is loading, unloading, handling, storage and also till the final consumption (Salin & Nayga Jr, 2003). This requires the cooperation of all the players involved in the distribution. Figure 2 below gives a holistic view of pharmaceutical and life science supply chain.

Figure 2: Holistic View of Pharmaceutical and Life Science Cold Chain



Source: (Reed, 2012a)

Freight Forwarder

Healthcare companies rarely communicate directly with the air carriers. They rely on their intermediaries such as their freight forwarder and third party logistics. While the burden for regulatory compliance mainly sits on the shoulders of the pharmaceutical companies, reliance is delegated as a shared responsibility through established partnerships. So they expect partners to operate with strong quality of management structure. Although there are hundreds of freight forwarders worldwide, only a select few of them have the experience to sufficiently handle the demanding requirements for health care products, especially if the shipments are time and temperature-sensitive. Some of the qualities that pharmaceutical companies look for in a freight forwarders are clear written agreement, clear understanding of the roles and responsibilities, performance monitoring, problem management (proper escalation procedures) and compensation & remedial actions (O'Donnell, 2011).

Some of the top freight-forwarding companies specialized in the field of cold chain are:

- LifeConEx (a joint venture between DHL and Lufthansa, headquartered in south Florida that handles only health care products).
- FedEx Custom Critical
- UPS Healthcare Solutions
- Others include Air Canada Cool Chain, Panalpina, Kuehne+Nagel, Schenker, UTI, Expediters etc.

It's the responsibility of the freight forwarder to choose the right solution (selection of the packaging system and the distribution process) for the pharmaceutical shipments rather than opting for the cheapest cargo solution. Thorough understanding of the air carrier's facilities and the individual customer's needs are required (Abscisse, 2011).

2.4 - INDUSTRY REGULATIONS

Due to several problems associated with this weak drug supply chain, both players from pharmaceutical industry and governments are looking for more stringent regulations (Wyld, 2008). While manufacturing of drugs are strictly controlled by the globally recognized 'Good Manufacturing Practices' (GMP), but transportation and distribution of these drugs are often uncontrolled or unregulated. The increased wastage has caught the attention of many countries' regulatory agencies. This change has led many countries to adopt their own *'Goods Distribution Practices (GDP)'*.

Good Distribution Practices (GDP) is basically an extension of Good Manufacturing Practices. It deals with the guidelines for the proper distribution of medicinal products for human use. GDP is a quality warranty system, which includes requirements for purchase, receiving, storage and export of drugs intended for the purpose of human consumption. This is the most recent regulation in the pharmaceutical industry (Abscisse, 2011).

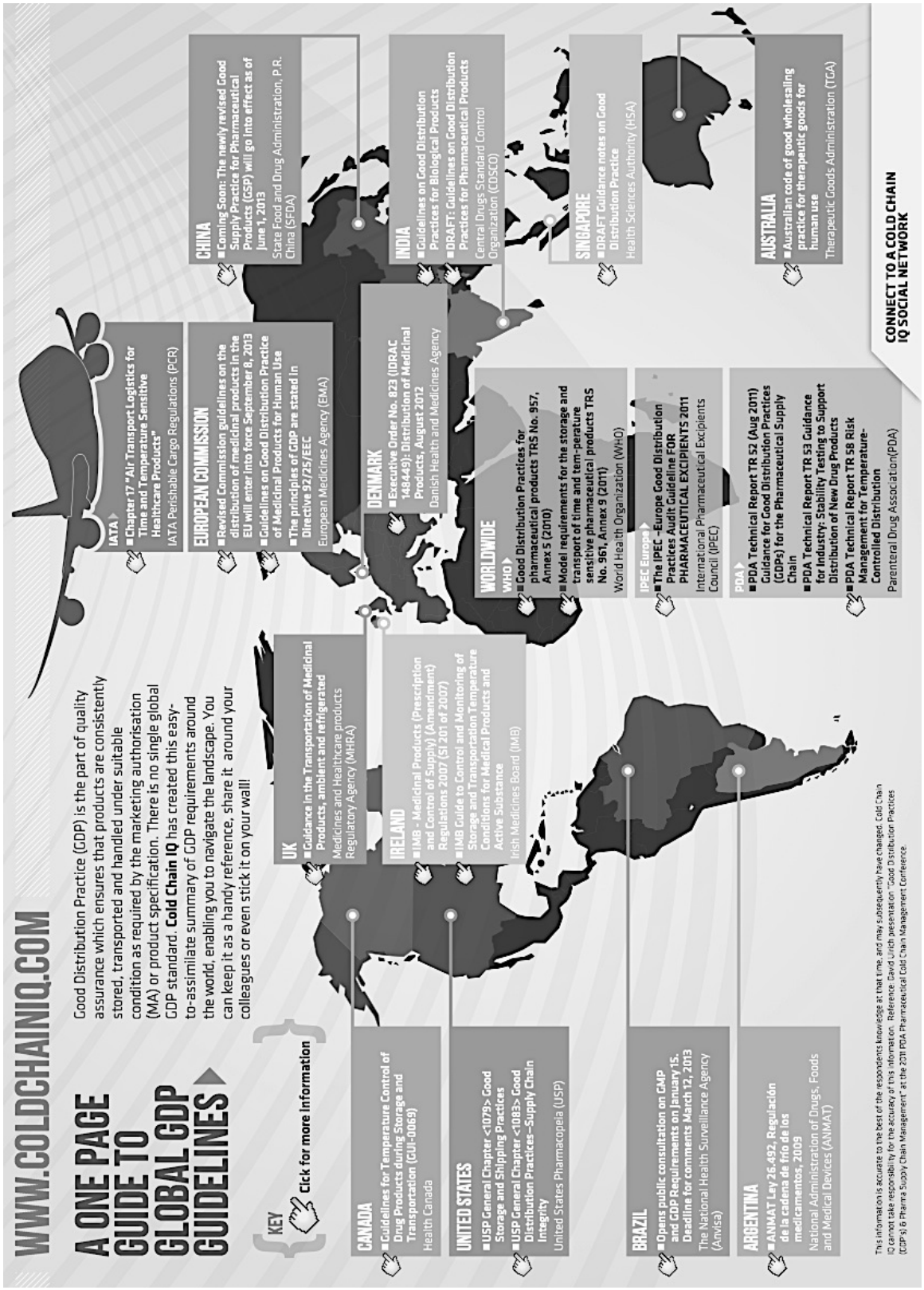
Below is a table with GDP Guidelines of different countries, regulatory bodies and related associations.

Table 3 – Different GDP Guidelines

USA	The United States Pharmacopeia (USP) Chapter <1079> Good Storage and Shipping Practices offers guidance and procedures on maintaining pharmaceutical integrity throughout the supply chain to the patient (USP, 2005).
Canada	Guide 0069 - Guidelines for Temperature Control of Drug Products during Storage and Transportation (HealthCanada, 2011)
European Countries	The European Union issued Guidelines <2013/C 68/01> on Good Distribution Practice of Medicinal Products for Human Use (EU, 2013)
World Health Organization (WHO)	The World Health Organization (WHO) provides WHO Technical Report Series, No. 937, 2006, Annex 5 which explains the Good Distribution Practices for Pharmaceutical Products (WHO, 2010)
The International Air Transport Association (IATA)	Effective July 1, 2007. International Air Transport Association (IATA) has added a chapter to the 7th Edition of the Perishable Cargo Regulations related to air transportation logistics (AACargo, 2010)

The map below is a one-page guide to the top GDP Guidelines globally along with their implementation dates.

Figure 3 – A One-Page Guide to Global GDP Guidelines.



Source: (Ulrich, 2011)

Problems due to differences in regulation among countries

The regulatory requirements and guidance for the storage and transportation of drugs varies according to the countries from which they originate. “Some are laws and some are guidance – strongly recommended suggestions that frequently include ambiguous words and phrases like “should” and “may;” “shall” and “will;” and “is, but is not necessarily limited to;” all of which can differ subtly enough in their meaning as to cause confusion across cultures where these drugs are transported” (O’Donnell, 2011, p. 49). Since each country has its own stringent GDP Guidelines, these regulations widely vary from country to country, and there is clearly a lack of uniformity. This divergence has proved challenging for the pharmaceutical manufacturers and all the supply chain agents. Earlier to this, pharmaceutical manufacturers had to voluntary take initiative to safeguard their product in order to avoid loss or maintain brand name. But with these new stringent regulations, they are forced to make sure that their distribution path is very planned & controlled (O’Donnell, 2011).

Difference between distribution models between USA & Canada

In USA, the supply chain integrators such as UPS and FedEx play a major role. They have highly efficient and reliable delivery networks that are often used by drug manufacturers and wholesalers for expedited delivery. Home healthcare services also rely on this network system of UPS for next-day and 2nd day shipments of medicines sent directly to patients’ homes, avoiding retail pharmacies altogether. They are even capable of reaching the most remote location of the country within a time frame of 24 hours. This drug distribution model is primarily a United States Model and is gaining attention in some Western European countries (O’Donnell, 2011).

In Canada, the distribution system is a little different. “The burden of regulatory responsibility is on everyone who takes ownership of transfer of the drugs during distribution, from manufacturers through to wholesalers and downstream to retailers. This is contrary to most countries where chain-of-custody is the responsibility of the drug innovator” (O’Donnell, 2011, p. 101). Since each cold

room is not centrally managed and other actors in the cold chain will not have a complete overview of possibly abusive events, local inspection is the responsibility of each partner in the supply chain (Hafliðason, Ólafsdóttir, Bogason, & Stefánsson, 2012). Since drug products are normally million-dollar shipments, no one in the chain wants to maintain ownership or responsibility any longer then they are forced to. This makes the distribution process very quick in Canada. The main challenges facing Canadians are uneven dispersion of its population, and extreme climate. Therefore a model has to be designed so that all provinces (whether Ontario, Quebec or Yukon) should be properly serviced, giving them equal access to medicines (O'Donnell, 2011).

Although USA & Canada have similar quality standards, Canada's GDP Guidelines are stricter than USA. Therefore goods traveling between these two countries will have to meet the Canadian GDP guidelines (Kohleriter, 2013).

2.5 – STANDARD OPERATING PROCEDURES (SOP)

In the face of a challenging regulatory environment, many pharmaceutical companies are striving to improve the quality of the drug shipment but at the same time trying to reduce the overall distribution costs. To achieve this goal, companies must first create a culture where quality objectives are transparent and well understood. This can only be achieved by following certain sets of procedures called as "Standard Operating Procedures" (Jain, 2008).

"Standard Operating Procedures (SOP) is a process document that explains in detail the way how an operator should perform a given operation. SOPs involve the purpose of the operation, the equipment and materials required, how to perform the set-up and operations required for the process, how to perform the maintenance and shutdown operations carried out by the worker, a description of safety issues, trouble-shooting, a list of spare parts and where to find them, illustrations, and checklists" (Akyar, 2012, p. 368). The development and use of SOPs are an integral part of a successful quality system. It provides information to an operator to perform a job properly and consistently in order to achieve pre-

determined specification and desired quality end-result (Jain, 2008). There are times when each customer may have different needs and requirements. In that case, when a standard set of Standard Operating Procedure (SOP) is insufficient to meet the customer's expectation, a more clearly defined (customized) SOPs must then be put in place (Abscisse, 2011).

2.6 - PROBLEMATIC AREAS IN COLD CHAIN

Below are the few areas where temperature excursion takes place more frequently:

a) Handover Points

There are concerns that the main fluctuation in temperature occurs at handover points. This calls for the need for additional care at handover points (Hafliðason et al., 2012).

b) Airport tarmac area

It has been reported that about 80% of the total journey of a shipment is spent waiting on the tarmac area and transportation to and from the airport (James, James, & Evans, 2006). Many feel the control of the shipment is lost upon arrival to the airport apron (tarmac). Here these shipments wait unprotected for too long a period of time. This issue is particularly serious during extreme weather conditions. Some tell that many airports do not have a temporary warehouse to store temperature-controlled products. Even if they have one, most of the time it is at full capacity. Other reasons could be the lack of awareness and knowledge about the specificity of the product by the handling ramp personnel (Abscisse, 2011). Development of a SOP will reduce the chances of such faults.

c) Customs delays – US Border

The recent decision by US Customs to screen all cargo has created another new level of uncertainty for drug shippers and freight forwarders. US-Customs and Border Protection can stop and search a cargo anytime it transits through the

United States. This increased the risk level of temperature excursion for these products transiting through the US. Some pharmaceutical drug manufacturers are also concerned regarding the effect of x-rays on the product. Many also try their best to avoid to transit through USA. This is not an ongoing problem, but when such events takes place it could create major problems in the distribution chain and threaten the integrity of the drug shipment (Abscisse, 2011).

> *"We have experienced delays of up to two weeks in shipping to countries outside of North America. Even though we were told the material was kept in a refrigerator during this time, at 2°C to 8°C, we discovered later that the temperatures actually fluctuated as high as 18°C". (Antonopoulos, 2014, p. 3)*

d) Clash between Incoterms & packaging system

In the cold chain, the Incoterms used in a trade can help in developing a temperature profile throughout its distribution circuit. This can help to understand just how long the package or system will have to be maintained in the desired temperature or environment. If the terms of the agreement are EXW (Ex Works), the seller makes the goods available at his/her premises (the medical laboratory). The buyer is responsible for collecting, uploading & transportation of the drug, hence bears the maximum risk till the final destination. Now, the question is who will be held responsible for the freight if the seller packs the product that encounters problems in transit even if the product was not mishandled? "Ethically speaking, we expect the seller should design the packaging in such a way that maintains the product integrity until the customer opens the container and not just to the point when they take possession legally" *(Antonopoulos, 2014, p. 3)*. So shipper should consider the impact of Incoterms on the drug shipment or the relationship with Incoterms with the packaging system. (Antonopoulos, 2014).

2.7 - COLD CHAIN EQUIPMENT

Beside organizational factors it is a generally agreed fact that cold chain equipment is the key factor in the well-functioning of the cold chain operations (Kreyenschmidt, Christiansen, Hübner, Raab, & Petersen, 2010). The use of advanced technologies has enabled informed decision-making, design of streamlined and secured networks (Narayana et al., 2014).

It is obvious that use of cold chain equipment can improve the maintenance of product quality and build a well functioning health care system, but it requires substantial capital investments (fixed or sunk cost) in storage and transportation facilities which are very costly to operate (Kuo & Chen, 2010) (Tetteh, 2009). So the type of cold chain technology to be used depends on the infrastructure of the partnering countries. Drug manufacturers have limitations in making direct investments in cold chain infrastructure throughout the value chain because of the nature of infrastructure as a public good (Salin & Nayga Jr, 2003). In Economics, a public good is a good that is non-excludable along social or geographic links (Bramoullé & Kranton, 2007). Road, highway, railways, reliable electric power supply systems, seaports are all public goods which are normally government owned (Salin & Nayga Jr, 2003). The lack of adequate infrastructure in most developing countries makes decision-making process of selecting the appropriate cold chain equipment and technology very vital. Equipment such as refrigerated containers, packaging system, cold storage, warehousing, refrigerated trucks are not usually under direct government ownership, but are essential for the well functioning of the cold chain. Mostly these infrastructures are privately owned either in-house or by cold chain service providers. At time when in-house facilities are not available, it is important that certain services should be hired from multiple sources. This makes cold chain infrastructure requirement very flexible. (Salin & Nayga Jr, 2003).

A reason why pharmaceutical companies have limited budget on building these physical infrastructure is because bulk of their financial resources are employed in building intangible infrastructure such as intellectual capital, research and

development (R&D) and other marketing efforts (Pedroso & Nakano, 2009). Drug manufacurers can reduce the repairs and maintenance costs by using existing older cold storage facilities & equipment, but it will be at the expense of quality (Salin & Nayga Jr, 2003).

The basic cold chain equipment includes:

a) Cold Chain transportation vehicles
b) Cold Chain temperature monitoring devices
c) Cold Chain packaging solutions

2.7.1 COLD CHAIN TRANSPORTATION VEHICLE

The main complexity of the distribution of biologics is due to the diverse modes of transportation available today, and their capability in controlling temperature. Various factors have to be considered in choosing the transportation mode such as time, cost, safety, risk of theft, risk of damage, distance, temperature control etc. Because logistics activities have shifted from manufacturing-oriented to consumer-oriented, the number of deliveries to customers have become more customized and increased in number. This has also increased the overall cost of transportation (Kuo & Chen, 2010).

Below are the few modes of cold chain transportation:

Road transportation. Using refrigerated trucks presents a good solution in the preservation of a defined temperature regime (Badurina & Majić, 2011). The trailer attached to the truck can also act as a secondary packaging (Rossetti, Handfield, & Dooley, 2011). Since the cost of operating a distribution center or warehouse is huge, managers are using intensive transportation as a remedy to reduce cost (Salin & Nayga Jr, 2003) which will serve as a cold storage area for the short term.

Air transportation proves to be difficult in terms of securing the required temperature regimes (due to connecting hubs, waiting time at the tarmac, customs, lack of infrastructure at the airport). In spite of this, air transportation is the most preferred mode for pharma companies for long-range shipping due to its

capability of covering longer distances in the shortest possible time, thus safeguarding the goods from being in transportation for a longer period of time (Badurina & Majić, 2011). Increased visibility of the transportation process is also achieved through air transportation. Since most shipments are multi-million dollar product, bio-pharma companies are ready to spend extra money in order to maintain their products and safeguard their brand name (Abscisse, 2011)

Ocean Transportation might be useful where low costs is a necessity and time-defined shipping is not prerequisite. But whenever sea freight are used, the mode of transportation has to changed as soon as the shipment reaches the port of arrival (country of destination) and this remains the critical point in realization (Badurina & Majić, 2011). Recently, there has been an increasing competition from ocean carriers due to the increase in the generic bio-similar drugs. Below are the few facts about ocean transportation:

Table 4 – Factors to consider for choosing ocean transportation

Reasons to choose ocean transport	***Reason not to choose ocean transport***
Many pharmaceutical and biotech manufacturers, particularly among generics and bio-similar manufacturers whose margins are considerably lesser that those of the big drug innovators are looking into ocean transport. Ocean cargo is typically 50%-70% cheaper than the cost of air cargo	Many ocean carriers are not ready to take the million-dollar liability risk. They avoid accepting expensive shipments.
Access to more effective containers with ships with less human intervention	Many ocean carriers are not ready to make heavy investment in new technology and refrigerated sea container.

Ocean transportation is used for large quantity shipment compared to air transportation.	Transportation time is lengthy, almost 3-5 weeks.
Earlier many pharma companies were hesitant in ocean cargo because of the increased shipping time & lack of visibility, however with new temperature monitoring devices and cooling equipment available on the market these days, ocean transportation is gaining popularity.	There are risks of mechanical failure while in ocean. Therefore close logistics monitoring is necessary. So this increase the shipper's requirement for constant supervision and maintenance.
It is the most environment friendly transportation mode. It emits the least carbon compared to airfreight, train & trucks	There is an increased environmental risk (temperature excursion) in ocean transportation such as exposure to extreme temperature, humidity & lack of security (theft).

Source : (Abscisse, 2011).

2.7.2 - COLD CHAIN MONITORING DEVICES

As training and adequate container alone does not guarantee a safe transportation (Abscisse, 2011), so proper monitoring and recording is a prerequisite for any cold chain logistics management system that aims at ensuring the product's quality at the customer's end (Wells & Singh, 1989). But with increased regulation from different regulatory organizations, there is an increased demand for standardized monitoring and traceability in the cold chain. In order to satisfy the customer's demands and to create a competitive advantage, it is necessary to have an automated and efficient monitoring at all level of operations (Heck & Vervest, 2007). Since the traditional approach of manual recording of information is cumbersome, it is necessary to have a better system for tracking and tracing.

Tracking means knowing the exact physical location of a particular drug shipment within the supply chain. And *tracing* means the ability to know their historical

location about a particular drug shipment such as location travelled, time spent in each location, record of ownership, packaging configuration etc. (Koh, Schuster, Chackrabarti, & Bellman, 2003). Wireless sensors network (WSN) technologies are now been used to implement real-time temperature monitoring (Hafliðason et al., 2012). These WSN are made of several small spatially dispersed sensor nodes, each with limited processing capacity and memory which will transmit date in the digital form to a base station (Akyildiz, Su, Sankarasubramaniam, & Cayirci, 2002). The base station collects data from multiple sensors and transmits this information to the central server. The advantages of using such continuous temperature monitoring devices is not only to maintain the product's quality and safety but also for economic reasons (Hafliðason et al., 2012). Below are few types of temperature monitoring devices:

Thermometers

The traditional practice of monitoring the vaccine temperature was done with the use of 'thermometer' (stem thermometer or bi-metal thermometer). But it is generally accepted fact that a thermometer cannot provide the adequate level of security. It can only be used for spot checks and it lacks the ability for continuous temperature monitoring. Hardly anyone can catch a cold chain excursion using a thermometer through a spot check. When comparing it with other temperature monitoring devices such as electronic data loggers, it has been discovered that there are large temperature discrepancies with the use of thermometers (Kartoğlu, Nelaj, & Maire, 2010).

Data Loggers

A data logger is an important part of the cold chain management solution. "It is a small cylindrical computer (approximate size of a vaccine vial) that records temperature at selected time intervals" (Wirkas et al., 2007, p. 692). The ability to record and store temperature at specific intervals during transportation helps the final end-user to determine if the shipment should be accepted or rejected (DeltaTrak, 2014). Pre-programmed data loggers are placed with the goods in a suitable position. Then after transportation, the data loggers are unpacked and

analyzed by specific software. This software produces a report including graphics for the duration of the journey that is often sent back to the shipper for review. The shipper is then able to make a judgment on the condition of the goods and provide authority to use. One of the most important factors in choosing a data logger is the accuracy of the data loggers. This is even more important if the objective is early detection of the temperature changes (Ruiz García & Lunadei, 2010).

Different types of Data loggers: (Bischof, 2013)

a) **Chemical Indicator Logger** – When the drug shipment faces a temperature excursion, there will be a change of color on the data logger. This will let the customer make a more informed decision on product quality and usability (TCP, 2014).

b) Chart Recorder – These data loggers draw the temperature during the transportation on the paper strip, indirectly creating a report (Dickson, 2012)

c) USB Logger – These data loggers store the temperature data in the USB memory, which can then be downloaded into the computer.

d) PDF Logger – It is same as USB Logger but creates a complete graphical and statistical data in PDF format. No web access is needed because information is stored in the USB. It is mainly used in the final destination. (Cryopak, 2014)

e) RFID Logger – It also stores temperature in the memory. But whenever there is a RFID reader around, data is automatically transfered. The disadvantage of this system is that it needs infrastructure along the supply chain, which is only possible if all the parties in the supply chain are ready to use this system.

f) Wi-Fi Loggers - These data loggers transmit the recorded temperature data wirelessly via a Wi-Fi network to a PC and can be viewed using a software package.

g) GSM Logger - Also stores temperature in the memory. But it communicates using a mobile network, whenever available. The disadvantage is that it cannot be used on airplane, as GSM should be switched off. There is a need for infrastructure to setup in advance for communication. Roaming charges will also apply. However this type of data logger are used for very important items where money is not a consideration at all (e.g. transportation of biological

weapons etc.).

Since different technical solutions (bar code or RFID data logger) can be used in a traceability system, a final choice has to be made based on the required data accuracy, reliability, and the general knowledge along the supply chain (Montanari, 2008).

RFID Data loggers

Traditionally most data-loggers required manual inspection which ended up being very costly (Abad et al., 2009). It was necessary to open individual containers and packages to retrieve information from each data-logger. Retrieved information about temperature variance of the product was only known at the end of the journey, which gave little opportunity for supply chain players to take any remedial action. For the well functioning of the cold chain, information should be available in real time. Reliable alert criteria should be set and communicated with all parties whenever the temperature goes out of bound (Hafliðason et al., 2012). A wireless sensor network (WSN) offers the opportunities for improved transportation planning (Ruiz-Garcia, Lunadei, Barreiro, & Robla, 2009) as this will combine both the RFID tags along with the data-logger technology. This will allow the entire cold chain stakeholders to have a near real-time temperature monitoring to take immediate decisions (Hafliðason et al., 2012). Therefore the use of RFID data loggers can be very helpful because it not only monitors and stores a detailed report of the temperature history, but this information can be transmitted accurately to all the parties involved in the cold chain such as suppliers, sponsors, final users etc near real-time . All these data will be linked with a computerized cold chain management system (Gras, 2006).

The new RFID data logger tags wirelessly sends the data via radio-frequency electromagnetic fields. Since scanning devices don't need a line of sight to detect RFID tags which are attached or embedded in the tracked product, users can remotely track and identify shipments (Sahin et al., 2007). Now-a-days RFID tags not only measure temperature, but also humidity (Chang, Kim, Kim, & Yoon, 2007) (Abad et al., 2009), shock/vibration (Todd, Phillips, Schultz, Hawkins, & Jensen,

2009) and also light (Abad et al., 2009; Cho, Song, Kim, Kim, & Yoo, 2005). The two main types of RFID tags are.

- **Passive RFID tags –** “Passive RFID tags can be as small as 0.3mm and don't require batteries. They are powered by the radio signal of a RFID reader, which alerts them to request a reply. Passive RFID tags can be read from a distance of about 20 feet. Semi-passive RFID tags contain a small battery that boosts the range. Passive tags are generally read-only; meaning the data they contain cannot be altered or written over” (Abscisse, 2011, p. 16).
- **Active RFID tags –** “Active RFID tags, also called transponders because they contain a transmitter that is always "on", are powered by a battery and are designed for communications up to 100 feet from the RFID reader. They are larger and more expensive than passive RFID tags, but can hold more data about the product and are commonly used for high-value asset tracking. Active RFID tags may be both read-write, meaning data they contain can be written over” (Abscisse, 2011, p. 16).

Placement of data-logger (Hafliðason et al., 2012)

Most operators use temperature monitoring devices to only track the ambient temperature and not the product temperature. This may be because of the difficulty of individually opening and placing the data-loggers in each box. Also, there is difficulty in retrieving these sensors from the small packages upon destination. Placement of these sensors is very critical for the monitoring. For example, sensors placed at the top or the side layers are more sensitive to temperature and experience larger fluctuations. Whereas, the sensors placed in the middle layer indicate relatively constant temperature.

Alert system

Alert system is one of the primary ways in which temperature variance can be brought to the attention of the decision-makers. The two most important types of alert systems in Wireless Sensor Network (WSN) are:

a) *Single Threshold Temperature Alert (STTA) – This* is the most common type of alert system. An alert is triggered the moment temperature reaches above

the prescribed threshold temperature. Here, the single input criterion is the temperature. (Hafliðason et al., 2012)

b) *Period based threshold temperature alert (PBTT)* – PBTT takes two inputs in consideration, which are 'the threshold temperature' and 'the predetermined period'. An alert is only triggered when the temperature is beyond the threshold temperature level for a predetermined period of time. This method is useful when an alert is only required when the situation is severe. (Hafliðason et al., 2012)

2.8 - COLD CHAIN PACKAGING SOLUTIONS

Packaging is an important factor for the proper functioning of the cold chain. The time constraint factor in transportation of healthcare products can also be eased (Salin & Nayga Jr, 2003) by using the appropriate packaging solutions. The type of insulation material used for transportation is one of the important variables that affects the temperature of products (Sharley et al., 2003). Various "layers" of packaging are built-up around a product that needs to be distributed. There are four groups of packaging: primary, secondary, tertiary and ancillary packaging components (O'Donnell, 2011).

1**) Primary, secondary and tertiary packaging** are part of standard processing steps, independent of whether temperature control is needed. These three types of packaging are used in any regular shipment. Primary packaging constitutes the first level of container for the vaccine. For example, vaccine vials. Secondary packaging is the intermediate packaging that contains the primary packaging. Tertiary packaging is the third level of packaging and is the outer box that contains the secondary packages (WHO, 2005).

2) **Ancillary packaging** components or systems refers to the transport packaging required to maintain specific temperature controlled transportation. This is the outermost containment. *Ancillary packaging systems are often divided in to two groups:*

a) Passive packaging system &

b) Active Packaging system

2.8.1 – PASSIVE PACKAGING SYSTEM

Passive packaging systems maintain a temperature-controlled environment inside an insulated enclosure, without thermostatic regulation. This is done by using a finite amount of pre-conditioned coolants such frozen gel packs, phase change materials (PCM), dry ice or others cold chain components (Howe, 2011). They are not controlled by any mechanical assistance or human intervention while in distribution. They have a predefined transport life and therefore they have to rely on a quick delivery. The shipment must be delivered quickly, not only because of the product's expiration dates but also due to the efficiency of the cool packages as most passive packaging system has maximum capacity of 48 hours only (Abscisse, 2011).

Passive packaging containers have many advantages such as a) cheap price because no refrigerator is required) b) less energy consumption because there are no fans) c) easy maintenance d) easy availability in the market. There are also some disadvantages such as a) inability to control the temperature b) inability of control temperature of large volume of products c) limited control of time in maintaining the desired temperature (Laguerre, Ben Aissa, & Flick, 2008). Various tests have proved that appropriate refrigerated shipping temperature could be maintained using straightforward passive packaging system consisting of frozen gel packs and insulated transit containers (Elliott & Halbert, 2005). When small volume of perishable product are to be transported within the domestic network with the use of non-refrigerated vehicles, passive systems are the best solutions (East et al., 2009). Some of the top passive packaging providers are ThermoSafe Brands (holds almost 60% market share), Cold Chain Technologies, AcuTemp, TCP Reliable, SCA Cool Logistics, Laminar-Medica & EnviroCooler.(O'Donnell, 2011).

PASSIVE PACKAGING COMPONENTS

Passive packaging components are devices or components that does not require external power source for its operation (maintaining the desired temperature). Below are the several passive packaging components used to maintain the desired temperature:

Dry Ice

Dry ice is often used for transporting temperature sensitive shipments because it can offer an extended cooling for the payload. Dry ice, which is solid carbon dioxide, can maintains a temperature of -78°C (-95°F). The main feature of dry ice is that it sublimates or changes directly from solid to gas, without a liquid phase. This does not cause any water leakage problem within the shipment. But the rate of sublimation required must be taken into account when designing a container system since it gets smaller in size. It is said that dry ice sublimates at a rate of three to eight pounds per day depending on the thermal properties of the container and external ambient/ temperature profile (Cold-Chain-Technologies, 2014). One should also be careful to check if the dry ice or its vapor have any adverse effect on the product or its primary package (Abscisse, 2011).

Gel Pack

In cold chain, the use of gel packs are a critical component of a thermal system. In most cases it is more important than insulation itself because they can provide the source of energy (and/or heat sink) that allows maintenance of temperature within an insulated container (Cool-Pack, 2014). Normally gel packs are plastic sac of ice, refrigerant gel, or liquid. These refrigerant components are usually non-toxic and can absorb a considerable amount of heat. It is specially developed in such a way so that it will not liquefy, leak or spill, and therefore will not spill easily or cause contamination if the container breaks to contaminate the product. These gel packs, like normal ice are frozen or chilled prior to their use. Initially, the gel-pack is placed in a freezer or other cooling system to reduce its internal temperature, and then it is used to keep other goods cool (Cellofoam, 2014). Gel packs can be reused and recycled. They are also compatible with all transportation system (Sofrigam, 2014a). Gel packs can be segregated in two main categories: rigid (or

bricks) and flexible bags (Cool-Pack, 2014)

a) **Rigid/Brick Gel Packs:** they come in the form of 'bricks'. These gel packs are ideal for use when rigidity or reusability is required. It also provides better reliable shape when frozen.
b) **Flexible Gel Packs:** these are the lowest cost type of gel packs. They cannot be reused and also got higher potential for leakage.

The numbers of ice gel pack employed in a shipment is also very important. Even though they are passive by nature, any additional usage of ice gel packs can bring the product's temperature to negative levels, thus cause freezing of the drug products. Some also use 'the welcome side effect' of pre-chilling the internal shipping environment with gel packs few hours in advance before the final parcel is placed (Elliott & Halbert, 2005).

Thermal Blankets

Thermal blankets are blankets with a certain insulation quality, which are used to insulate or protect temperature sensitive goods such as pharmaceuticals and other perishables products. Thermal blankets are commonly used in airfreight as part of the passive packaging solution to protect the temperature-sensitive goods against unwanted external temperatures and weather conditions. The thermal blankets can be used as a wrapping foil or can be tailor-made. (TEMAX).

Phase Change Materials (PCM)

Since temperature-sensitive health care products are regularly shipped throughout the year, they are exposed to a wide range of temperatures. Even though they are shipped in insulated containers and controlled environments (temperature profile of the distribution circuit), the temperature stability of the shipping containers can be significantly improved by applying suitable thermal energy storage approach (Rentas, Macdonald, Houchens, Hmel, & Reid, 2004). Phase Change Materials (PCM) is material that undergoes a phase change (solid form to liquid form or vice-versa) at a specific temperature. The energy is stored during its melting stage and is recovered from its storage during the freezing stage (Li, Xue, Ding, Han, & Sun, 2009). This gives it a great capacity to absorb

the latent heat and also slowly use that energy for the cooling purpose.

2.8.2 – ACTIVE PACKAGING SYSTEM

Active packaging systems are powered using electricity or other fuel source to maintain a temperature-controlled environment inside an insulated enclosure under thermostatic regulation. Examples include cold rooms, refrigerators, temperature-controlled trucks, refrigerated containers (Howe, 2011). The top active packaging solution providers in market today are Envirotainer and C-Safe.

Envirotainer

Envirotainer has received EASA approval (Europe) after several years of effort, but failed to receive FAA approval (USA) for its e-1 containers (which both heat and cool). In spite of this issue, Envirotainer is still the largest provider of active containers with 95% of the active system container market (O'Donnell, 2011). Envirotainer has adopted one of the strongest temperature-controlling cargo solutions in the industry by setting its own QEP accreditation program. Under this program, each airliner carrier has to go through the accreditation process in various locations around the world. The objective is to provide shippers (drug manufacturers) with assurance that handling of their product in each location will meet industry guidelines set forth by the pharmaceutical industry. An extensive hands on training is also provided to all its members (airlines carriers) internationally. This training will give all the cargo personnel an understanding of all the aspects of how to control, operate, maintain and troubleshoot situations. An example would be training the cargo personnel on complete operation of the control panel of the container, changing dry ice, managing cooling system, battery replacement etc. (AACargo, 2010).

C-Safe

Envirotainer's main competitor, *CSafe,* has a similar program called 'Enhanced Qualified User Program' (EQUiP). This program is developed to help companies meet CSafe's compliance requirements and to bring a high level of confidence among users of the container. Accreditation is awarded to those companies who fulfill the compliance to an assessment program. This includes successful

completion of a Web-based training by an authorized EQUiP company representative (O'Donnell, 2011).

Table 5 - Advantages & Disadvantages of Active Packaging System

Advantages	Disadvantages
No warehousing required to store the container after use because the unit (active container) is typically leased, not owned.	Since product is leased, availability can be an issue (i.e., active flu season, typical increase in bulk vaccine shipments)
Highly secure. It reduces the risk of theft.	Limited lane segments; may not be able to ship to all destinations.
Quick loading/unloading; less labor intensive.	When a pharmaceutical company has one of these shippers delivered, every piece of that mechanical unit should be verified, because every time it is used, to some degree it changes. This has become a sensitive issue. End-users are suppose to verify if all the components work as they did when the container was first qualified in a test lab.
Environmentally friendly; no need to dispose of non-biodegradable packing materials. Packaging system is reused under a close-loop system.	Relies on batteries, compressors, generators, thermostats, and fans. These energy sources can wear out or break down. Sometime, there is also risk of freezing of the product due to mechanical issues
Cost effective when payload is maximized; ideal for large bulk shipments.	Not cost effective if payload is too small; end up paying for empty space

Source: (Vaczek, 2006)

Table 6 - Advantages & Disadvantages of Passive Packaging System

Advantages	Disadvantages
Less regulated and easy to qualify.	Cannot handle extreme temperature.
Certain configurations may have reverse logistics capabilities for reuse.	Refrigerant must be conditioned according to specifications.
Can be shipped anywhere in spite of peak seasons or not.	Warehousing required
Eliminate the chance of mechanical risk (mechanical failure)	Limited transport life.

Source: (Vaczek, 2006)

2.9 DECISIVE FACTORS IN CHOOSING A PACKAGING SOLUTION

Below are some of the decisive factors considered when choosing a packaging solution:

1. **Size of the drug shipment**

   The size and weight of the shipment have to justify the use of refrigerated container (active packaging vs. passive packaging). A drug manufacturer can use an active refrigerated container if the size and weight of the drug shipment are large. But if the shipment is small in size, the shipper may have to consider using a passive packaging system (Sofrigam, 2014b).

2. **Cost of the drug**

   Drug manufacturers are ready to spending extra money for the distribution process for the best and safest transportation system (Abscisse, 2011). This might be because of these drugs' expensive value.

3. **Distance**

   If the distance of transportation is long, then generally an active packaging system is preferred as it provides more transport life than a passive packaging

system. However if the transportation distance is short, then a passive packaging system would be preferred.

4. **Cost of packaging**

   It includes all cost connected with the preparation, transportation and use of the packaging system. Active packaging systems are more expensive, and passive systems are less expensive. (Romero, 2013; Sofrigam, 2014b).

   However due to the tough economic times and highly competitive market these days, many companies are becoming more cost conscious and are looking for different ways to minimize cost. When it comes to transportation of temperature-sensitive drugs, pharmaceutical companies could think of reducing their cost by using cheaper packaging solutions such as passive packaging solutions, but this comes at the risk of exposing the products to the ambient temperature. These minor cost saving might be attractive in the short term but all those savings can be wiped out if a single shipment faces a critical temperature excursion before it reaches the final user (Grubb, 2013). On the other hand, many companies also ignore the possibility that their packaging system might be over-engineered. This over-engineering comes at an additional price that can increase the overall cost of the distribution process. Therefore it is advisable for companies to perform a test on a regular basis (Kohleriter, 2013) on their spending and search for cheaper solutions whenever possible, without harming the quality of the drug.

5. **Temperature range requirement of drug**

   Temperature range requirement of each drug is specified by the drug manufacturer's laboratory. Some drugs may have wider temperature range than others. Drugs having a narrow temperature range requirement will need more care than drugs with wider temperature range. If the particular drug has a very narrow temperature range requirement (e.g. from 2-8 degree Celsius), then an active packaging system is more useful than a passive one (Romero, 2013). But in case when the drug's temperature range is large (e.g. 5-20 degree Celsius), using a passive container would be possible.

6. **Temperature accuracy requirement of the drug**

   'Temperature accuracy requirement of the drug' is also specified by the drug manufacturer's laboratory too. Some drugs irrespective of their temperature range requirement may have less or more tolerance level to temperature excursion. The factor 'Temperature accuracy requirement of the drug' is different from 'Temperature range requirement of the drug'. The former recommends the temperature range within which the drugs must be maintained and the latter explains the level of tolerance accepted outside the recommended temperature range. Drugs with strict temperature accuracy requirement will be transported through an active packaging system (because the temperature accuracy requirement range is very narrow), whereas drugs with less strict temperature accuracy requirement could be transported by passive packaging system (because the temperature accuracy requirement range is wider).

7. **Distribution circuit**

   The distribution of medicine starts from the drug manufacturer's laboratory. The package can be shipped directly to the consignee site by using direct flights, or the package can be shipped to a central hub for sorting & grouping process based on geographical zones. Also there are several possible combinations of intermodal transportation (truck, railway, sea or air). The actual distance travelled may increase or decrease depending on the distribution circuit selected. In the case of air transportation, if the drug has to transit through connecting hubs where there is no refrigerating facility, then the manager has to take alternative actions. (Sofrigam, 2014b)

8. **Shipper's concern about the flexibility of the packaging system to change to unexpected ambient temperature during transportation**

   Active packaging systems provide the greatest flexibility when a shipment is exposed to a temperature profile different from the qualification temperature profile. (Romero, 2013). However, passive packaging system cannot cope to the unexpected ambient temperature.

9. **Shipper's concern about the reliability of the packaging system during transportation**

   Since active packaging systems are run by mechanical force, batteries and external power supply, there always exist a chance of mechanical failure. On the other hand, since passive packaging systems are not controlled by any mechanical force, it has less chance of mechanical failure or breakdown (Romero, 2013). Therefore passive packaging is considered to be a more reliable system than active packaging systems.

10. **Shipper's concern about the supervision and maintenance requirement during transportation**

    Active systems are easy to set up but may require constant check-up (supervision) and maintenance during the transportation/ transit process depending on the length of the distribution process. On the other hand, passive packaging requires a lot of work during the setup stage (like pre-conditioning and assembly procedures), but they do not require any maintenance while in transit. There is an 'Ease of Set-up' vs. 'Ease of Maintenance' factor to be looked into (Romero, 2013).

11. **Risk of hazardous concern due to the use of a particular packaging system**

    The risk connected with the materials used should be taken into consideration for selecting the ideal packaging solutions (Romero, 2013). Active systems are run by external power supply or lithium batteries, which are more hazardous. On the other hand, passive packaging systems use gel packs or Phase Change Materials (PCM) which are less hazardous.

12. **Impact on environment**

    Different packaging solutions can have a different impact on the environment. This may include all the materials and energy used for the preparation and maintenance of the packaging system during its life cycle (Sofrigam, 2014b). Active systems follow a close-looped distribution process where transportation containers have to come back for reuse. However passive systems have two options such that it can be reusable or can be disposed. We have also noticed

the packaging manufacturers' increased concern about the environment when designing a packaging solution. (Sofrigram, 2014)

3. METHODOLOGY

We understood that in cold chain, the quality of service is heavily dependent on the investment in modern technologies and equipment. These cold chain technologies and equipment include different types of refrigerated containers, temperature monitoring devices, time-temperature integrators (TTI) and cold chain packaging solutions. Several studies have been dedicated to various areas of the cold chain such as cold chain networks (Salin & Nayga Jr, 2003), use of time-temperature integrators (Sahin et al., 2007), temperature-monitoring devices (C. Nelson et al., 2007; Abad et al., 2009; Akyildiz, Su, Sankarasubramaniam, & Cayirci, 2002), and coping with GDP regulations pertaining to the distribution of these temperature-controlled products (O'Donnell, 2011), etc. But very little attention has been given to the area of cold chain packaging system, which is an important cold chain equipment that can help to minimize the wastage that occurs during the transportation process.

As we narrowed our research towards the cold chain packaging system, we looked into greater detail the various factors that influence managers to choose among the alternative packaging solutions. Decisive factors for selection of a packaging system include both quantitative and qualitative factors. Quantitative factors (size and weight of the drug shipment, distance between the country of origin and destination', 'temperature requirements' etc.) were easy to understand, but the inclusion of qualitative factors ('shipper's concern about the supervision and maintenance requirement', 'shipper's concern about the reliability of the packaging system during transportation', 'shipper's concern about risk of hazard during transportation', and 'shipper's concern about environmental impact etc.) makes it difficult for managers to make uniform decisions. Even in the same business, different managers cultivated different mental models of the same situation. This plurality of mental modes among managers of the same industry leads to differences in opinion with respect to the same given situation (Kassing,

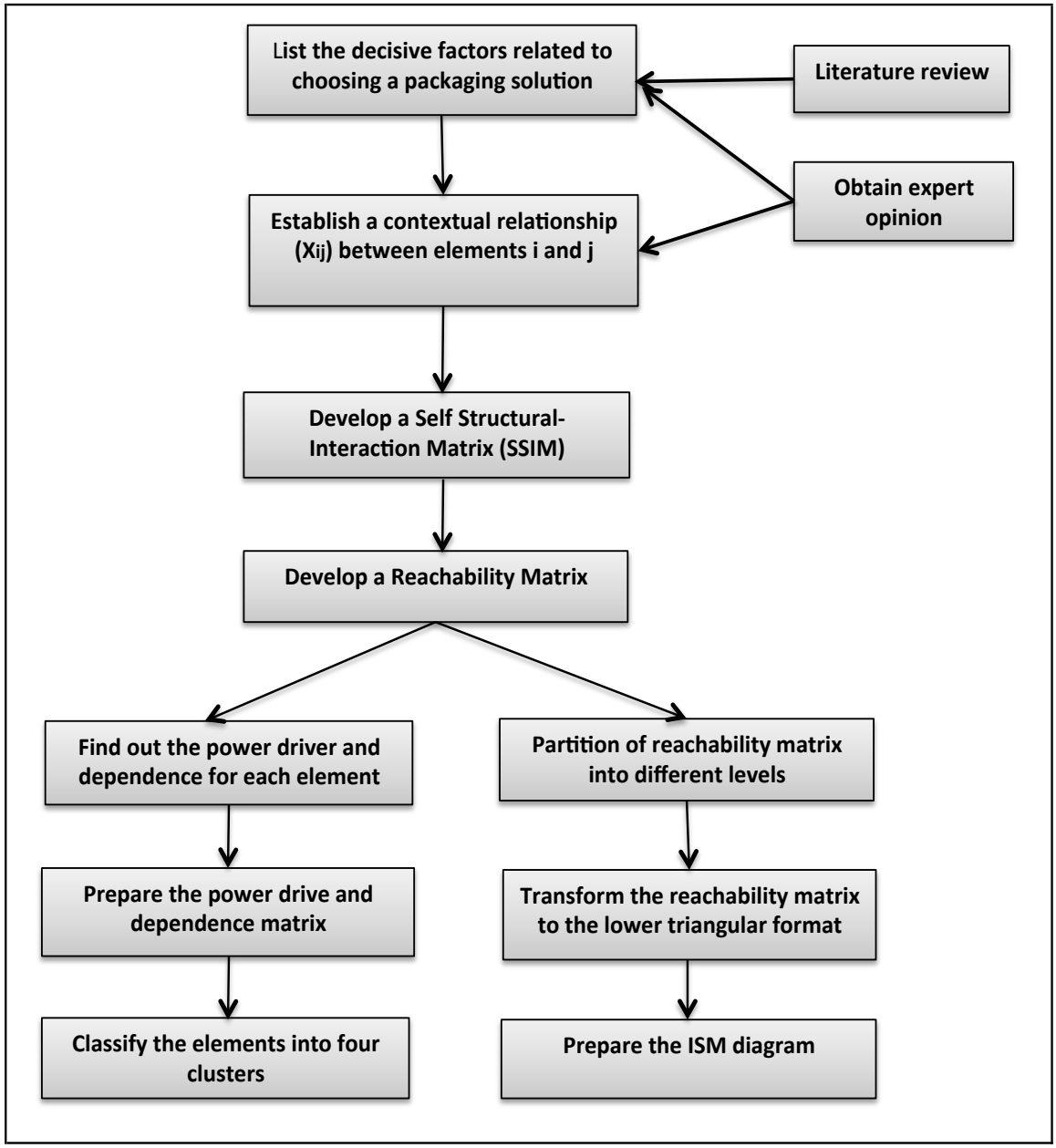
2001). Even in the cold chain distribution, each company adopts different packaging solutions based on their individual manager's judgment. These judgments may be an outcome of several factors such as the managers' history, memory, experience, anticipation, foresight, goal and values (Dagum, 1986). Some researchers have developed appropriate 'think-tools' methodologies where qualitative factors can be expressed in mathematical terms in the form of binary relations (Bolanos, Fontela, Nenclares, & Pastor, 2005). Therefore, we decided to use a powerful methodology called 'Interpretive Structural Modeling' (ISM) in order to better understand the packaging decision making process.

The main goal of ISM methodology is to assist decision makers in understanding what he/she really believes in and to recognize clearly what he/she does not know (Attri, Dev, & Sharma, 2013). When using this methodology, the participants can develop a deeper understanding of the meaning and significance of each decision element and the interrelations between these elements (Attri et al., 2013; Janes, 1988). It will also show the drive power and dependence of each factor (Mandal & Deshmukh, 1994). Understanding the direct and indirect relationship between these decisive factors will show the situation far more accurately than an individual factor taken in isolation, giving the user a clear insight into the collective understanding of these relationships (Attri et al., 2013). One advantage of the ISM methodology is that it communicates the result to the user in the combination of words and diagrams based on mathematics, but mathematics are hidden. ISM uses discrete mathematics logic and structure such as binary numbers, matrix theory, Boolean algebra etc. to demonstrate the relationship between elements (Janes, 1988). It should be understood that ISM methodology is only a tool for determining order in decision making (flow of ranking) and direction on a complexity of relationships among different elements (Ravi & Shankar, 2005). It does not assign weightage to any element (Govindan, Palaniappan, Zhu, & Kannan, 2012). This is because each company could assign different weightage for each factor. For example, different companies may have different sets of value for environmental standards.

We now briefly refer to several studies conducted with the help of ISM methodology. Many researchers have applied ISM methodology in order to understand complex problems. Pfohl, Gallus, & Thomas, 2011 used ISM to support risk managers in identifying and understanding interdependencies among supply chain risks on different levels. Bolanos et al., 2005 applied ISM in clarifying the perception of different individuals in a managerial group in order to improve group decision-making. Ravi & Shankar, 2005 have used ISM to identify, rank and understand the interrelation between the many barriers to reverse logistics in the automobile supply chain. Azevedo, Carvalho, & Cruz-Machado, 2013 has used ISM to identify and rank the performance measures to support the evaluation of automotive supply chain performance. Govindan, Kannan, & Haq, 2010 has used ISM to analyze the interaction between the attributes in selection of third party reverse logistics provider (3PRLP). Mandal & Deshmukh, 1994 used ISM methodology to analyze the most important vendor selection criteria and showed the interrelationship and their levels. Sharma & Gupta, 1995 applied ISM methodology to identify the key variables to develop a hierarchy of actions required in achieving the future needs of the waste management system in India.

Figure 4 illustrates a flow chart on the application of the ISM methodology. It is a customized version adapted from several papers (Attri et al., 2013; Govindan et al., 2012; Mandal & Deshmukh, 1994).

Figure 4 – Flow Chart on application of ISM Methodology



3.1 STEPS TO FOLLOW FOR THE APPPLICATION OF ISM METHODOLGY

1. **Decide on the type of ISM structure to be chosen** - Warfield, 1994 has defined several ISM structural types depending on the elements class and relation types requirement such as objective, goals, budgeting, problem etc. Table 7 shows the different ISM structural types. Among the various ISM structure types, the most appropriate one relating to a given research topic has to be chosen. In our case, 'Intent Structure' will be used, where decisive factors can be ranked in order of influence. It will produce a result (ISM Diagram) that shows what factors will influence other factors. In that way, we can see the different stages (levels) of the decision-making process.

Table 7 – Different ISM Structural types

Type of structure	Element class	Relation type	Specific relation(s) used in applications
Intent structure	Objectives, goals, intentions	Influence	"Supports", "helps achieve"
Priority structure	Budget line items	Comparative	"Is of equal or higher priority than", "is equal or higher value than"
DELTA chart	Activities, events decisions	Temporal	"Should precede or coincide with"
Problematique	Problems	Influence	"Aggravates"
Curriculum sequence	Learning modules	Temporal	"Should be learned before or coincident with"
Solution sequence	Unknown variables	Influence, temporal	"Is a function of", "should be computed before"
Field	Option	Definitive	"Is in the same category as"
Design quad	Dimension	Influence, temporal	"Is dependent on", "should be explored first in making design choices"
Complementary	Any	Any	"Is the complement of"

Source: Warfield (1994, p. 62)

2. **Choose participants (industry experts) with specific knowledge about the content –**

   In order to investigate a complex problem through an ISM methodology, a team has to be formed with four categories of people as follows:

   a) Stakeholders – People who will be affected by the outcome of the investigation. In our case, we will use the drug manufacturer and the freight forwarder (used by the same drug manufacturer). So they both are stakeholders of same supply chain.
   b) Specialist (expert) - It is desirable to request the help of a group of people such as industry experts who have specific knowledge about the content and the issue of the study. In our case, we will approach a freight forwarder who is independent to the previous stakeholders' supply chain. This is to get an independent unbiased opinion.
   c) Facilitator – Someone can take the participants through the various step of the ISM methodology process. In our case, it will be the researcher.
   d) Structural Modelers – Someone who can work with the participants in structuring the issues and finding the solution. In our case, it will be the researcher.

   The selection of the participants will totally depend on the situation. However, literature suggest that the group size of the participants should be limited to eight people because as the group size increases much above this level, the quality of the responses deteriorates (Janes, 1988).

3. **Find the elements (factors) related to the question** – This step includes identifying the different variables which are relevant to the issue (Attri et al., 2013; Govindan et al., 2012) . These sets of elements (factors) can be collected from various literatures. In this thesis, the elements would be the various decisive factors used by managers in making a cold chain packaging decision.

4. **Administrating a questionnaire to validate the identified factors** – Even though we have obtained these factors from reliable literature, it is more desirable to generate and validate these elements from participants in the form of questionnaire or personal interview (Attri et al., 2013; Debnath & Shankar, 2012; Janes, 1988). Here the researcher should try to make the participant suggest new elements that may be missing in the literature. Also, unwanted elements can be removed as per the instructions of the participants.

5. **Prepare a Structural Self-Interaction Matrix (SSIM)** – Once we have gathered all the important elements to the problem, a Structural Self-Interaction Matrix (SSIM) is developed based on the pairwise comparison of these elements. ISM methodology suggests the use of various techniques such as brain storming either from experts in industry or in academia to identify the contextual relationship among the factors (Debnath & Shankar, 2012; Govindan et al., 2012; Ravi & Shankar, 2005). This process will indirectly force the participants to state explicitly the interrelations between them (Janes, 1988). For understanding the contextual relationship, a 'leads to' or 'influences to' must be chosen. This shows that one factor influences the other factor. (Attri et al., 2013).

In our case, the question asked will be 'Will decisive factor 'i' influence factor 'j'?

In order to analyze the relationship among the elements, a contextual relationship will be developed by four symbols (V, A, X and O). These symbols denote the relationship between factors i and j:

- V: if decisive factors 'i' will influence decisive factors 'j';
- A: if decisive factors 'j' will influence decisive factors 'i';
- X: if decisive factors 'i' and 'j' will influence each other; and
- O: if decisive factors 'i' and 'j' do not influence each other.

6. **Reachability matrix –** From the SSIM, the relationship among factors will be transformed into a binary matrix called the ‘reachability matrix’. The relationship among factors is translated into binary numbers as follows: (Govindan et al., 2012)

   − If the (i, j) entry in the SSIM is V, then the (i, j) entry in the reachability matrix becomes 1 and the (j, i) entry becomes 0.

   − If the (i, j) entry in the SSIM is A, then the (i, j) entry in the reachability matrix becomes 0 and the (j, i) entry becomes 1.

   − If the (i, j) entry in the SSIM is X, then the (i, j) entry in the reachability matrix becomes 1 and the (j, i) entry also becomes 1.

   − If the (i, j) entry in the SSIM is O, then the (i, j) entry in the reachability matrix becomes 0 and the (j, i) entry also becomes 0.

7. **Level Partitions Iteration –** From the reachability matrix, ‘the reachability set’ and ‘the antecedent set’ of each factor can be found. A ‘reachability set’ consists of the factor itself and the other factors it affects, whereas the ‘antecedent set' consists of the factor itself and other factors which reach to it. The element that has the lowest assignment in ‘reachability set’ and the highest assignments in the ‘antecedent set’ will be placed on the top of the ISM diagram because these top-level factors will not influence any factor. Once the top-level factor is identified, it should be removed from the table and the level partition iteration process would start all over again until the level of each factor is determined. It is this level partition iteration process that helps building the ISM diagram (Ravi & Shankar, 2005).

8. **Transform the reachability matrix to a triangular format (conical) matrix –** The power drive of the factor is derived by summing up the number of 1s in the rows and its dependence power by summing up the number of 1s in the columns. The highest power drive ranks are given to the factors with the maximum number of 1s in the rows and columns (Attri et al., 2013). This will be useful in generating the MICMAC analysis.

9. **MICMAC Analysis–** The objective of the MICMAC analysis is to understand the individual characteristics of each element by analyzing their driving power and dependence power (Govindan et al., 2010). All the factors will be classified into four clusters based on their driving power and dependence. The dependence variable will be plotted on the y-axis of the graph. The driving power will be plotted on the x-axis of the graph. The graph will be divided into four clusters as follows:

Table 8 - Characteristics of each cluster in the MICMAC Analysis

Clusters	**Characteristics**
Independent variables	High driving power and low dependence
Linkage variables	Strong driving power and strong dependence
Autonomous variables	Weak driving and weak dependence
Dependent variables	Weak driving power but strong dependence

By knowing which factors have more driving power and dependency, one could pay more attention to these factors.

10. **Display the ISM Diagram –** Once the matrix is complete, a final multi-level ISM diagram from the matrix is prepared. In the development of the diagram, the most influential factors will be placed at the bottom of the diagram, and the least influential factors will be placed at the top of the diagram. Ranking or numbers will be assigned to each level. The higher the number, the higher the influence.

4. DATA COLLECTION PROCESS

4.1 - Selection of participants and their role

For expert opinion, the following cold chain participants will be approached and their roles will be as follows:

a) Drug manufacturers – Data collection for SSIM

b) Freight forwarder 1 – Data collection for SSIM

c) Freight forwarder 2 - Final validation and independent feedback on the results generated

Since each participant plays a different role or works for a different company within the cold chain, we were able to receive feedbacks from different perspectives, thus reducing biased opinion. These participants were selected because they had significant decision-making power and had expert knowledge about selecting a cold chain packaging solution.

4.2 – Interview process

A questionnaire was prepared and administered for each expert. The researcher (thesis student) presents the objective of the study to the participant and clarified the definition of each element. The researcher will act as both a facilitator and also a modeler. He played the role of a facilitator to guide the participants during the ISM session and also keep them focused on the specific issues to ensure the most productive use of the participants' time (Janes, 1988). He should also actively participate by giving necessary instructions and support the expert during the completion of the questionnaire.

Our goal was to get the opinions from the industry expert in order to fill our SSIM and Reachability Matrix. But this can only be achieved if we are able to make them understand the true benefits of answering these questions. So we took initiative by spending the first few minutes to explain to the participants how ISM methodology worked and what kind of results we can expect from it. Therefore, we used the example from a recent research paper that employed ISM methodology.

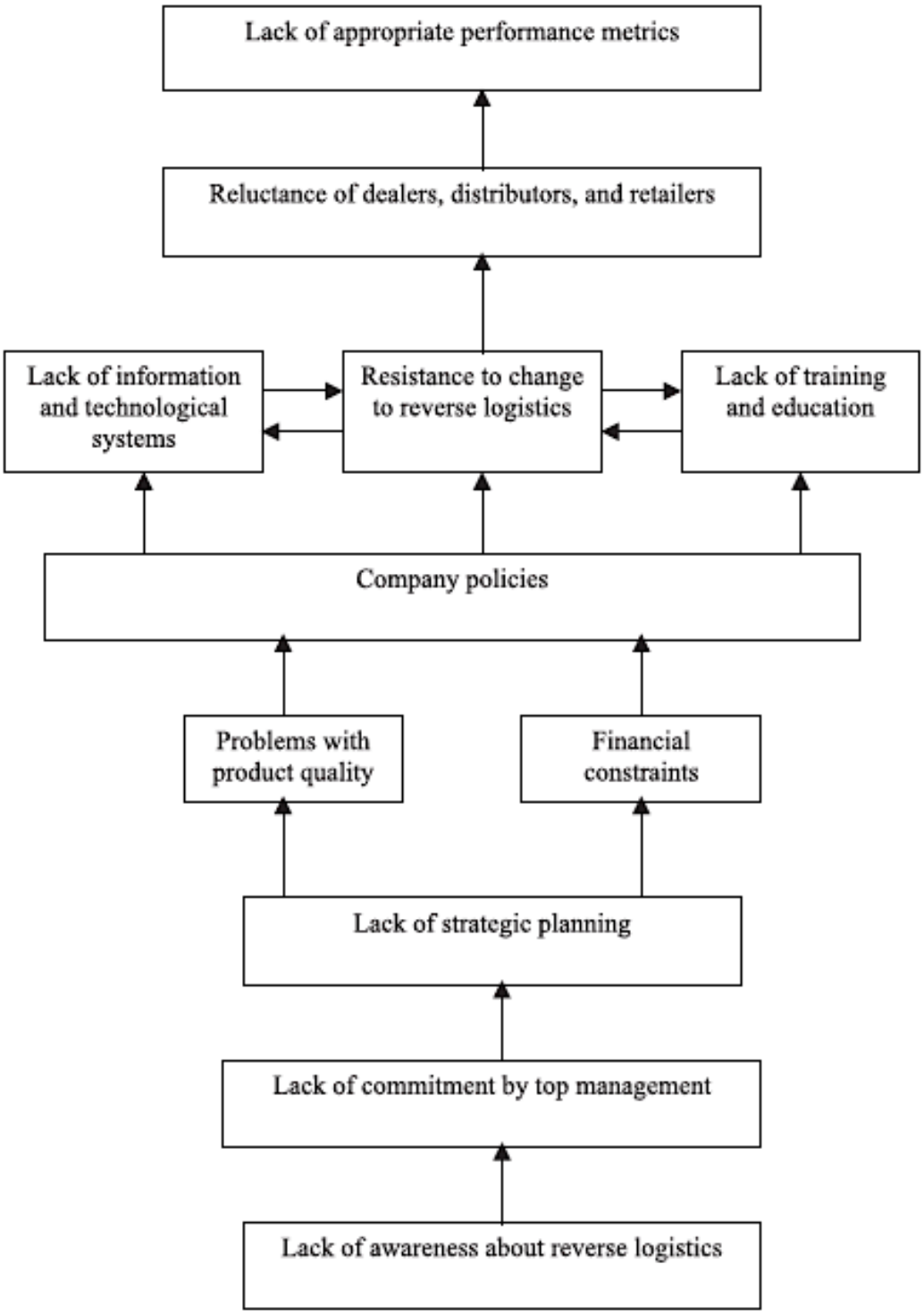
4.2.1 – Example of a research paper that employed ISM methodology

V. Ravi, Ravi Shankar, 2005 used ISM methodology to analyze the major barriers that hinder or prevent the application of reverse logics in automobile industries. Through a brainstorming session and various interviews, it is understood that the various barriers in implementing a reverse logistics system in an automobile industry which were as follows:

1. Lack of information and technological systems
2. Problems with product quality
3. Company Policies
4. Resistance to change to reverse logistics
5. Lack of appropriate performance metrics
6. Lack of training and education
7. Financial constraints
8. Lack of commitments by top management.
9. Lack of awareness about reverse logistics
10. Lack of strategic planning
11. Reluctance of the support of dealers, distributors, and retailers.

By increasing the participants' size, it is possible to generate and understand the meaning the different barriers. But it will be hard for anyone of them to identify the root cause of each barrier. Most people will only have a few barriers in mind and might ignore the others. But with the help of an ISM Methodology, decision makers can have a better idea of the elements he/she believes in and also recognize many things he did not know. The final result (ISM Diagram) depicted in Figure 5 was shown to our participant.

Figure 5 - Results generated by the sample research paper using ISM methodology



ISM-based model for the barriers of reverse logistics.

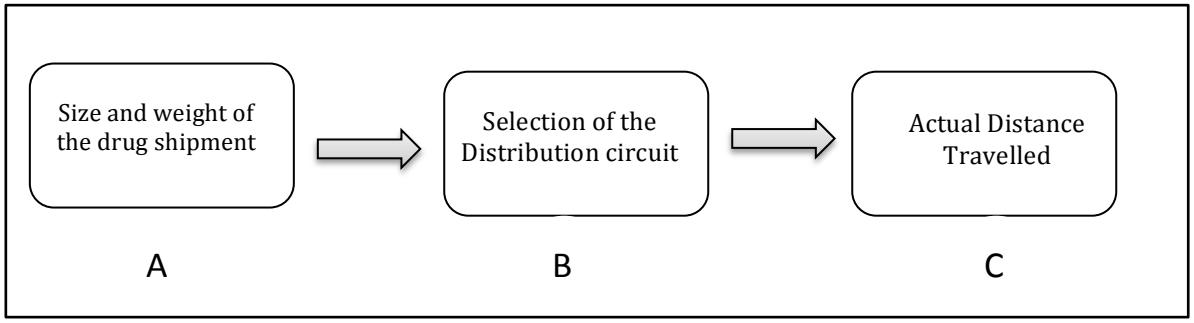
Source: (Ravi & Shankar, 2005)

The above ISM Diagram shows the actual root cause to various barriers in implementing a reverse logistics solutions. If one would ask an employee of the company trying to implement reverse logistics about his/her views on the barriers to reverse logistics, they might mention one or two elements such as 'lack of information technology system' or 'lack of training' or 'no cooperation from supply chain partners etc.' but they won't know the exact root cause of the problem. But an ISM Diagram clearly shows the whole problem in the most simplistic way that can help managers understand where to focus.

Our participants were convinced with the reliability and the usefulness of this methodology. They were now much more interested in participating in our interview, as they were curious to discover the final result. So this approach was very useful to gain the participant's interest in our study.

The participants were asked to take into consideration the concept of transitivity while responding to our questions. Transitivity is the basic assumption used in an ISM approach (Raj, Shankar, & Suhaib, 2008). The concept of transitivity can be explained through an example as follows:

Figure 6 - Effect of transitivity



Source: Self-prepared

Factor A 'size and weight of the drug shipment' can influence Factor B 'selection of the distribution circuit'. The type of 'distribution circuit' chosen can influence Factor C 'actual distance travelled by the shipment'. So the concept of transitivity

assumes that Factor A can indirectly influence Factor C too. Therefore, our participants are asked to take this into consideration when responding to our questions.

An extensive time was required with the industry participants to complete our SSIM. We were granted an interview session ranging from 60-90 minutes from each participant. Considering the time allotted for our interview, we have decided to divide our SSIM between two participants. However this multiple stages of meetings with participants turned our interview process from a structured to a semi-structured interview method. In a structured interview, the interviewer asks a rigorous set of questions that does not allow the interviewee to divert or think outside the box. But in a semi-structural interview, the interviewee is given the opportunity to recommend new ideas that the interviewer may not have thought about (Yin, 2009). So we were able to test one interviewee's recommendation with our subsequent participants.

Use of Independent industry expert (Freight forwarder) for validation

A third industry expert was also approached to validate our results. This participant has to be independent from the other two participants. The sole purpose of such a meeting was to check the results from an outside perspective so that there was no conflict of interest. We selected a freight forwarder that was an expert in the field of distribution of temperature-sensitive pharmaceutical products. During the meeting, the participant was asked the following:

a) Verification of the placement of each factor at their respective levels (Level 6 through Level 1).
b) Explain the link (flow) between factors in one level to the factors in the subsequent level.
c) Suggestion for addition or elimination of any factors.
d) Usefulness of our results from the point of view of the industry expert.

Their opinions will be explained in the analysis section of the thesis.

4.3 – Data Collection

Participant 1 – Drug Manufacturer

Our main objective of conducting an interview with the drug manufacturer was to understand how they looked at the cold chain packaging decision-making process. Since the drug manufacturer is the most powerful and ultimate decision makers in this chain, we wanted to see what they felt were the most important decision factors. Certain information on factors such as influence of the 'cost of the drug' on the packaging decision and the company's concern about the safety of the drug shipment are more known to the drug manufacturers. The allotted time for our interviewer with the drug manufacturer was 60 minutes. We met the person in-charge of transportation who had significant decision-making power in choosing a cold chain packaging solution.

For the drug manufacturer, we have prepared two types of questionnaires:

a) The first questionnaire (Questionnaire #1 - Drug Manufacturer in Appendix 1) was used to help us complete the cells in the SSIM (Figure 7 - SSIM for Drug Manufacturer). In order to use the expert's time more wisely, we decided to only ask a few questions (the grey shaded cells). The rest will be kept for the drug manufacturer's freight forwarder who granted us more time for interview.

b) A second questionnaire (Questionnaire #2 - Drug Manufacturer in Appendix 2) was also prepared that was not directly related to our ISM methodology, but it was intended to understanding overall decision-making process in the cold chain packaging, with that company's perspective in particular. This may be helpful in understanding the existing decision-making process and compare it with our work.

Figure 7 - SSIM for Drug Manufacturer

STRUCTURAL SELF-INTERACTION MATRIX (SSIM)

	i	12	11	10	9	8	7	6	5	4	3	2	1
j	Decisive factors in choosing packaging system	Impact on environment	Risk of hazard during transportation	Maintenance and supervision requirement during transportation	Reliability of the packaging system	Flexibility of the packaging system to change to unexpected ambient temperature	The distribution circuit	Temperature accuracy requirement of the drug	Temperature range of the drug	Cost of packaging	Distance to be travelled	Cost of the drug	Size and volume of the shipment
1	Size and weight of the drug shipment	O	O							V		O	
2	Cost of the drug	O	O	O	O	O	O	O	O	O	O		
3	Distance to be travelled	O	O							V			
4	Packaging cost	O	O				A	A	A				
5	Temperature range of the drug	O	O										
6	Temperature accuracy requirement of the drug	O	O										
7	The distribution circuit	O	O		X								
8	Flexibility of the packaging system to change to unexpected ambient temperature	O	O										
9	Reliability of the packaging system	O	O										
10	Maintenance and supervision requirement during transportation	O	O										
11	Risk of hazard during transportation	O											
12	Impact on environment												

In order to analyze the relationship among the elements, a contextual relationship will be developed by four symbols (V, A, X and O). These symbols denote the relationship between factor i and j:

- V: if decisive factors 'i' will influences decisive factors 'j';
- A: if decisive factors 'j' will influences decisive factors 'i';
- X: if decisive factors 'i' and 'j' will influence each other; and
- O : if decisive factors 'i' and 'j' does not influence each other.

Only the shaded items outlined above in the SSIM were asked to the drug manufacturer. Their individual responses were filled in the shaded cells during the interview. The explanation for individual assignment is outlined in Table 9 - Explanation for individual assignment on SSIM Matrix.

In addition to filling the cells in the SSIM, **the drug manufacturer** also suggested elimination and addition of certain factors. Factors that were eliminated were 'cost of the drug' (2), 'shipper's concern about the risk hazard during transportation' (11) and 'shipper's concern about the impact on the environment' (12). So, these factors were removed. The added factor was 'Product type'. The reasons for the elimination and the addition will be explained in our final analysis section in order to avoid repetition.

The relationship of the new factor 'Product type' with all other factors involved in the study has been filled out as follows:

Figure 8 - Addition of new factors by drug manufacturer

STRUCTURAL SELF-INTERACTION MATRIX (SSIM)
For Drug Manufacturer (Addition of new factor)

	i	13	12	11	10	9	8	7	6	5	4	3	2	1
j	Decisive factors in choosing packaging system	Impact on environment	Risk of hazard during transportation	Maintenance and supervision requirement during transportation	Reliability of the packaging system	Flexibility of the packaging system to change to unexpected ambient temperature	The distribution circuit	Temperature accuracy requirement of the drug	Temperature range of the drug	Cost of packaging	Distance	Cost of the drug	Size and volume of the product	Product type
1	Product type	O	O	V	V	V	V	V	V	V	V	O	V	-

Participant 2 – Freight Forwarder 1

During interview with the drug manufacturer, we confirmed the fact that freight forwarders were the most important partners of the drug manufacturer when it came to distributing these temperature sensitive drugs. Even though the drug manufacturer had the ultimate decision making power, they relied heavily on the suggestion given by the freight forwarder. It may be because the drug manufacturers feel that the freight forwarder specializing in the distribution of temperature-sensitive products have more knowledge about the packaging solutions. So we expected to get a lot more information from the freight forwarder. Therefore it was necessary to request the freight forwarder for additional interview time. The allotted time was 90 minutes.

At the beginning of the interview process, the Director of the company spent around fifteen minutes giving a brief introduction to their company, the various cold chain equipment used such as temperature monitoring devices, the distribution process, the different types of packaging systems etc. Then we introduced our research topic, question, and the proposed methodology.

Figure 9 - SSIM for Freight Forwarder 1

STRUCTURAL SELF-INTERACTION MATRIX (SSIM)
Questionnaire for Freight Forwarder

	i	10	9	8	7	6	5	4	3	2	1
j	Decisive factors in choosing packaging system	Shipper's concern about the reliable functioning of the packaging system during transportation	Shipper's concern about the supervision and maintenance requirement during transportation	Shipper's concern about the capacity of the packaging system to be flexible to unexpected ambient temperature	Packaging cost	Selection of distribution circuit	Distance to be travelled	Temperature excursion tolerance level	Temperature range requirement of the drug	Product type	Size and weight of the drug shipment
1	Size and weight of the drug shipment	V	V	O	V	V	V	O	O	A	-
2	Product type	V	V	V	V	V	V	V	V		
3	Temperature range requirement of the drug	V	V	V	V	V	V	O			
4	Temperature excursion tolerance level	V	V	V	V	V	V				
5	Distance to be travelled	X	X	V	V	X					
6	Selection of distribution circuit	X	X	V	V						
7	Packaging cost	A	A	A							
8	Shipper's concern about the capacity of the packaging system to be flexible to unexpected ambient temperature	O	O								
9	Shipper's concern about the supervision and maintenance requirement during transportation	X									
10	Shipper's concern about the reliable functioning of the packaging system during transportation										

In order to analyze the relationship among the elements, a contextual relationship will be developed by four symbols (V, A, X and O). These symbols denote the relationship between factor i and j:
- V: if decisive factors 'i' will influences decisive factors 'j';
- A: if decisive factors 'j' will influences decisive factors 'i';
- X: if decisive factors 'i' and 'j' will influence each other; and
- O : if decisive factors 'i' and 'j' does not influence each other.

The grey shaded areas in Figure 9 were the cells that were not asked to the previous participants (drug manufacturer), so this was asked to the freight forwarder 1. Their individual responses are filled in the shaded cells during the interview process. The explanation for individual assignment is outlined in Table 9 - Explanation for individual assignment on SSIM Matrix.

At the end of the interview, interviewee was given the opportunity to make recommendations to improve our research. The freight forwarder suggested addition of two new factors that we were not aware of. They were ‘Shipper’s concern about the temperature profile of the country of origin and destination’ and ‘Time to market’. The importance of these factors will be explained in our final analysis in order to avoid repetition. Below is the relationship of the two new factors with the rest of the existing factors.

Figure 10 - Addition of new factors by Freight Forwarder 1

STRUCTURAL SELF-INTERACTION MATRIX (SSIM)
For Freight forwarder (For addition of new factors)

Decisive factors in choosing packaging system	Shipper's concern about the reliable functioning of the packaging system during transportation	Shipper's concern about the supervision and maintenance requirement during transportation	Shipper's concern about the capacity of the packaging system to be flexible to unexpected ambient temperature	Packaging cost	The distribution circuit	Distance to be travelled	Temperature excursion tolerance level	Temperature range requirement of the drug	Product type	Size and weight of the drug shipment	Time to market	Concern about the temperature profile of the origin and destination country
Concern about the temperature profile of the origin and destination country	V	V	V	V	V	V	A	A	A	O	O	-
Time to market	V	V	O	V	V	V	O	O	O	O	-	O

4.4 – Compilation of the data

All the information collected from the participants was compiled into a single SSIM Matrix as shown below in Figure 11. The explanation for individual assignment is outlined in Table 9.

STRUCTURAL SELF-INTERACTION MATRIX (SSIM)

	i	12	11	10	9	8	7	6	5	4	3	2	1
j	Decisive factors in choosing packaging system	Shipper's concern about the reliable functioning of the packaging system during transportation	Shipper's concern about the supervision and maintenance requirement during transportation	Shipper's concern about the capacity of the packaging system to be flexible to unexpected ambient temperature	Packaging cost	Selection of distribution circuit	Distance to be travelled	Time to market	Shipper's concern about the temperature profile of the origin and destination country	Temperature excursion tolerance level	Temperature range requirement of the drug	Product type	Size and weight of the drug shipment
1	Size and weight of the drug shipment	V	V	O	V	V	V	O	O	O	O	A	-
2	Product type	V	V	V	V	V	V	O	V	V	V		
3	Temperature range requirement of the drug	V	V	V	V	V	V	O	V	O			
4	Temperature excursion tolerance level	V	V	V	V	V	V	O	V				
5	Shipper's concern about the temperature profile of the origin and destination country	V	V	V	V	V	V	O					
6	Time to market	V	V	O	V	V	V						
7	Distance to be travelled	X	X	V	V	X							
8	Selection of distribution circuit	X	X	V	V								
9	Packaging cost	A	A	A									
10	Shipper's concern about the capacity of the packaging system to be flexible to unexpected ambient temperature	O	O										
11	Shipper's concern about the supervision and maintenance requirement during transportation	X											
12	Shipper's concern about the reliable functioning of the packaging system during transportation												

In order to analyze the relationship among the elements, a contextual relationship will be developed. Four symbols (V, A, X and O) will be used. These symbols will denote the relationship between factor i and j:

- V: if decisive factors 'i' will influences decisive factors 'j';
- A: if decisive factors 'j' will influences decisive factors 'i';
- X: if decisive factors 'i' and 'j' will influence each other; and
- O : if decisive factors 'i' and 'j' does not influence each other.

Detailed explanations for each assignment is found in the section 'Explanation for individual assignment on SSIM Matrix'

Figure 11 - Final SSIM

Table 9 - Explanation for individual assignment on SSIM

1	Size and weight of the drug shipment			Source
1-2	Product type	SINGLE EFFECT (A)	The 'size of the drug shipment' cannot influence the 'product type'.	DRUG MANUFACTURER
			The 'product type' (blood components or vaccines) could have a small influence on the overall 'size of the drug shipment'. Some product type such as blood components are transported in larger quantity, but whereas product types such as biologics (vaccines) are usually transported in smaller quantity.	
1-3	Temperature range requirement of the drug	NO EFFECT (O)	- The 'temperature range requirement of the drug' is specified by the drug manufacturer's laboratory. So 'the size and weight of the drug shipment' cannot influence 'the temperature range requirement of the drug'.	FREIGHT FORWARDER 1
			- 'The temperature range requirement of a particular drug' cannot influence (change) 'the size and weight of the drug shipment'.	
1-4	Temperature excursion tolerance level	NO EFFECT (O)	- 'The temperature accuracy requirement of each drug' is specified by the drug manufacturer's laboratory. 'The size and weight of the drug shipment' will have no effect on 'the temperature accuracy requirement of a drug'.	FREIGHT FORWARDER 1
			- 'The temperature accuracy requirement of a drug' cannot change 'the size and weight of the drug shipment'.	
1-5	Shipper's concern about the temperature profile of the origin and destination country	NO EFFECT (O)	- 'The size and weight of the drug shipment' cannot influence 'the shipper's concern about the temperature profile of the country of origin and destination'.	UNRELATED
			- 'Shipper's concern about the temperature profile of the origin and destination country' cannot influence (change) 'the size and weight of the drug shipment'.	
1-6	Time to market	NO EFFECT (O)	- 'The size and weight of the drug shipment' cannot influence the drug manufacturer's urgency to introduce the product to market on time ('time to market').	UNRELATED
			- The drug manufacturer's urgency to bring the product to market on time ('time to market') cannot influence 'the size and weight of the drug shipment'.	
1-7	Distance to be travelled	SINGLE EFFECT (V)	- 'The size and weight of the drug shipment' can indirectly effect 'the actual distance travelled'. Freight forwarder has mentioned that they experienced several situations where the shipment was too large in size. Hence, they were unable to load it into a particular aircraft, therefore they had to use an alternative aircraft. This changed the distribution circuit. A change in the distribution circuit will indirectly increase or decrease 'the actual distance travelled by the shipment'.	FREIGHT FORWARDER 1
			- 'The distance travelled' by the drug shipment cannot the change' the size and weight of the drug shipment'.	

1-8	Selection of distribution circuit	SINGLE EFFECT (V)	- 'The size and weight of the drug shipment' can directly influence 'the distribution circuit selected by the shipper'. As mentioned in the previous cell (1-7), freight forwarder has mentioned that they experienced situations where the shipments were larger in size in order to load into a particular aircraft (passenger airplane). Therefore they had to use an alternative aircraft (cargo airplane). So this explains how 'size and weight of the shipment' can influence 'the shipper's selection of the distribution circuit'. - 'The distribution circuit selected by the shipper' cannot influence 'the size and weight of the drug shipment'.	FREIGHT FORWARDER 1
1-9	Cost of packaging (Active vs. Passive system)	SINGLE EFFECT (V)	- 'The size and weight of the drug shipment' has a strong influence on the type of packaging system used, hence it will effect 'the cost of the packaging'. E.g. If 'the size of the drug shipment' is small then the shipper cannot justify the cost of using an active container (which is normally large in size and expensive), therefore a passive container (which is normally smaller in size and inexpensive) will be preferred. But if 'the size and weight of the drug shipment' is large, then the shipper would use an active container because they can justify the cost of using an active container. The drug manufacturer mentioned that 'size of the drug shipment' was one of the main factors considered while making packaging decision. - 'The cost of packaging' (i.e. selection between an active or passive packaging container) cannot change 'the size and weight of the drug shipment'.	DRUG MANUFACTURER & FREIGHT FORWARDER
1-10	Shipper's concern about the capacity of the packaging system to be flexible to unexpected ambient temperature	NO EFFECT (O)	- 'The size and weight of the drug shipment' cannot influence 'the shipper's concern about the capacity of the packaging system to be flexible to the changing ambient temperature'. - 'The capacity of the packaging system to be flexible to the changing ambient temperature' cannot influence 'the size and weight of the drug shipment'.	FREIGHT FORWARDER (I)
1-11	Shipper's concern about the supervision and maintenance requirement during transportation	SINGLE INDIRECT EFFECT (V)	- The size and weight of the drug shipment can indirectly influence the maintenance and supervision required during transportation. If the size and weight of the shipment is large, then the shipper would use a different distribution circuit that can increase or decrease the supervision availability. - Maintenance and supervision required during transportation cannot change the size and weight of the drug shipment.	FREIGHT FORWARDER (I)
1-12	Shipper's concern about the reliable functioning of the packaging system during transportation	SINGLE INDIRECT EFFECT (V)	- 'The size and weight of the drug shipment' can indirectly effect 'the shipper's concern about the reliable functioning of the packaging system'. If the size and weight of the shipment is larger than expected, then the shipper would use a different distribution circuit. This can indirectly increase the concern about the reliable functioning of the packaging system. For example, if the product is distributed through a connecting hub that has got extreme weather, then this concern will certainly increase. - 'The shipper's concern about the reliable functioning of the packaging system during transportation' cannot change 'the size and weight of the drug shipment'.	FREIGHT FORWARDER (I)

2	Product type			Source
2-3	Temperature range requirement of the drug	SINGLE EFFECT (V)	The drug manufacturer has mentioned that 'product type' was one of the key factor considered before taking a packaging decision. Since each 'product type' got similar temperature requirements, one can make a close assumption of the care and attention required. For example, 'Product types' such as vaccine has lower temperature range requirements, whereas blood components have a wider temperature range requirement. So 'the temperature range requirement of the drug' is dependent on 'the product type'.	DRUG MANUFACTURER
			'The temperature range requirement of the drug' cannot change 'the product type'.	
2-4	Temperature excursion tolerance level	SINGLE EFFECT (V)	The drug manufacturer has mentioned that 'product type' was one of the main factor considered before taking a packaging decision. Each product type have similar 'temperature excursion tolerance level'. So one can make a close assumption of 'the temperature excursion tolerance level of the drug' by its 'product type'. For example, Product types such as vaccine has lower temperature excursion tolerance level, whereas blood components have a wider temperature excursion tolerance level.	DRUG MANUFACTURER
			'The temperature accuracy requirement of the drug' (temperature excursion tolerance level) cannot change 'the product type'.	
2-5	Shipper's concern about the temperature profile of the origin and destination country	SINGLE EFFECT (V)	The product type' of the drug' can influence 'the shipper's concern about the temperature profile of the origin or destination country'. If the drug's 'product type' is very delicate and requires a more controlled temperature then, the shipper will be more keen to study about the temperature profile.	FREIGHT FORWARDER (I)
			'Shipper's concern about the temperature profile of the origin or destination country' cannot change 'the product type'.	
2-6	Time to market	NO EFFECT (O)	'The product type' of the drug cannot influence the drug manufacturer's urgency to bring the product to the market on time (time to market).	FREIGHT FORWARDER (I)
			A drug manufacturer's urgency to bring a particular drug to the market (time to market) cannot change the 'product type'.	
2-7	Distance to be travelled	SINGLE EFFECT (V)	'The product type' of the drug can have an indirect effect on the 'distance to be travelled' by the drug shipment. If the product type of the drug belongs to a very delicate product category such as vaccines or insulin etc., the freight forwarder will consider selecting a safer distribution circuit. This can increase or decrease 'the actual distance travelled by the shipment'.	DRUG MANUFACTURER
			'The distance to be travelled by the drug shipment' cannot change 'the product type'.	

2-8	Selection of distribution circuit	SINGLE EFFECT (V)	'The product type of the drug' can have an direct effect on 'the distribution circuit selected by the shipper'. If the product type of the drug belongs to a very delicate category such as vaccines or insulin etc., the freight forwarder will transport it through a quicker or safer distribution circuit.	DRUG MANUFACTURER
			'The distribution circuit selected by the shipper' cannot change 'the product type'.	
2-9	Cost of packaging (Active vs. Passive system)	SINGLE EFFECT (V)	'The product type of the drug' can influence 'the cost of packaging' (type of packaging system to be used) . During the interview, the drug manufacturer mentioned that 'Product type' was one of the main factors considered before deciding on a cold chain packaging system.	DRUG MANUFACTURER
			'The cost of packaging system' (type of packaging solution selected) cannot change 'the product type'.	
2-10	Shipper's concern about the capacity of the packaging system to be flexible to unexpected ambient temperature	SINGLE EFFECT (V)	If 'the product type' is very delicate, then 'the shipper's concern on the capacity of the packaging system to be flexible to unexpected ambient temperature' will increase.	DRUG MANUFACTURER
			'The shipper's concern about the capacity of the packaging system to be flexible to unexpected ambient temperature' cannot change 'the product type'.	
2-11	Shipper's concern about the supervision and maintenance requirement during transportation	SINGLE EFFECT (V)	Certain 'product types' are more regulated than others and require mandatory supervision. So 'the product type of the drug' can influence' the shipper's concern about the supervision and maintenance required during the transportation'.	DRUG MANUFACTURER
			'The shipper's concern about the supervision and maintenance required during transportation' cannot change 'the product type'.	

2-12	Shipper's concern about the reliable functioning of the packaging system during transportation	SINGLE EFFECT (V)	'The product type' are more delicate than others and requires more care and attention. A little bit temperature excursion can damage the product. The freight forwarder narrated us about situations where some airport hubs didn't have appropriate power socket to charge their active containers while on transit. Therefore, they were unable to recharge them. In another situation, active container stopped functioning as there were kept in the airport tarmac area when there was extreme cold ambient temperature (approx. -40 degree Celsius). This really increased the risk of mechanical failure. On the other hand, if the shipper choses a passive container that is not controlled by any mechanical force, it got less chance of any mechanical failure or breakdown, so even though they have less transport life and cannot change to unexpected ambient temperature, they are more reliable when it comes to proper functioning. So the nature of 'the product type' can increase or decrease 'the shipper's concern about the reliable functioning of the packaging system'.	DRUG MANUFACTURER, FREIGHT FORWARDER (I)
			'The shipper's concern about the reliable functioning of the packaging system' cannot change 'the product type'.	

3	**Temperature range requirement of the drug**			**Source**
3-4	Temperature excursion tolerance level	NO EFFECT (O)	- 'The temperature range requirement of the drug' cannot change 'the temperature excursion tolerance level of the drug' that is specified by the drug manufacturer's laboratory.	UNRELATED
			'The temperature excursion tolerance level of the drug' cannot change 'the temperature range requirement of the drug'.	
3-5	Shipper's concern about the temperature profile of the origin and destination country	SINGLE EFFECT (V)	'The temperature range requirement of the drug' can influence 'the shipper's concern about the temperature profile of the origin and destination country'. If the drug has a small and narrow temperature range requirement (ranging from 5 to 8 degree Celsius), then the shipper will surely be keen to know about the temperature profile of the origin and destination country. If the temperature range requirement of the drug is large, then the shipper will be less concern about the temperature profile of the country of origin and destination.	FREIGHT FORWARDER (I)
			'Shipper's concern about the temperature profile of the origin and destination country' cannot change 'the temperature range requirement of the drug' that is specified by the drug manufacturer's laboratory.	
3-6	Time to market	NO EFFECT (O)	'The temperature range requirement of the drug' cannot influence the drug manufacturer's urgency to bring the product to the market on time (time to market).	FREIGHT FORWARDER (I)
			'The time to market' strategy by the drug manufacturer cannot change 'the temperature range requirement of the drug'.	

3-7	Distance to be travelled	SINGLE EFFECT (V)	'The temperature range requirement of the drug' can indirectly influence 'the distribution circuit used by the shipper'. If the temperature range requirement of the drug is very narrow, then the shipper might use a distribution circuit that is very safe. For example, connecting hubs with have good infrastructure, trained equipment operator, less tarmac waiting time etc. Selection of different distribution can indirectly increase/decrease 'the actual distance travelled by the drug shipment'.	FREIGHT FORWARDER (I)
			'The distance travelled by the shipment' cannot change 'the temperature range requirement of the drug'.	
3-8	Selection of distribution circuit	SINGLE EFFECT (V)	The temperature range requirement of the drug' can influence 'the distribution circuit used by the shipper'. As per the freight forwarder, if the temperature range requirement of the drug is very narrow, then the shipper might use a distribution circuit that is very safe. For example, connecting hubs with have good infrastructure, trained equipment operator, less tarmac waiting time etc. If the temperature range requirement is very wide, then the shipper will be open to most distribution circuits.	FREIGHT FORWARDER (I)
			'The distribution circuit of the shipment' cannot change 'the temperature range requirement of the drug'.	
3-9	Cost of packaging (Active vs. Passive system)	SINGLE EFFECT (V)	The temperature range requirement of the drug' can influence shipper's 'cost of packaging' (Active Vs. Passive packaging system). If the temperature range requirement of the drug is wide, the shipper will use a passive packaging system which may be less expensive. But if the temperature range requirement of the drug is very narrow, the shipper may use an active packaging system that may increase 'the cost of packaging'. During the interview, the drug manufacturer mentioned that the temperature range requirement of the drug was one of the main factor considered while making a packaging decision.	DRUG MANUFACTURER
			'Cost of packaging system' (Active Vs. Passive) cannot change 'the temperature range requirement of the drug'.	
3-10	Shipper's concern about the capacity of the packaging system to be flexible to unexpected ambient temperature	SINGLE EFFECT (V)	'The temperature range requirement of the drug' got an indirect effect (influence) on 'the shipper's concern about the capacity of the packaging system to change to unexpected ambient temperature'. If the temperature range requirement of a drug is narrow, then the shipper will be more concern about the temperature profile. If the temperature profile of the distribution circuit has enough environmental risk, then it will influence the shipper to be more concerned about 'the capacity of the packaging system to be flexible to unexpected temperature'.	FREIGHT FORWARDER (I)
			'Flexibility of the packaging system to cope with unexpected ambient temperature' cannot influence 'the temperature range requirement of the product'.	

3-11	Shipper's concern about the supervision and maintenance requirement during transportation	SINGLE EFFECT (V)	The freight forwarder mentioned that all temperature-controlled shipments requires constant supervision during transportation.	FREIGHT FORWARDER (I)
			'The supervision and maintenance requirement of the packaging system during transportation' cannot change 'the temperature range requirement of the drug'.	
3-12	Shipper's concern about the reliable functioning of the packaging system during transportation	SINGLE EFFECT (V)	If 'the temperature range requirement of the drug' is narrow, then it will influence the shipper to be more concern about 'the reliable functioning of the packaging system during transportation'.	FREIGHT FORWARDER (I)
			'The shipper's concern about the reliable functioning of the packaging system during transportation' will not change 'the temperature range requirement of the drug'.	

4	**Temperature excursion tolerance level (The temperature accuracy requirement of the drug)**			**Source**
4-5	Shipper's concern about the temperature profile of the origin and destination country	SINGLE EFFECT (V)	'The temperature excursion tolerance level of the drug' can influence 'the shipper to be more concern about the temperature profile of the origin and destination country'. If the drug's temperature excursion tolerance level is small (strictly between +/- 2 degree), then the shipper will be more concern to know about the temperature profile of the origin and destination country. On the other hand, if the drug's temperature excursion tolerance level is high (+/- 15 degree), then the shipper will be less interested to know about the temperature profile of the origin and destination country.	FREIGHT FORWARDER (I)
			'Shipper's concern about the temperature profile of the origin and destination country' will not change 'the temperature excursion tolerance level of the drug'.	
4-6	Time to market	NO EFFECT (O)	'The temperature excursion tolerance level of the drug' cannot influence the drug manufacturer's urgency to bring the product to the market on time (time to market).	FREIGHT FORWARDER (I)
			The shipper's urgency to the bring the product to the market on time (time to market) cannot change 'the temperature excursion tolerance level of the drug'	
4-7	Distance to be travelled	SINGLE EFFECT (V)	'The temperature excursion tolerance level of the drug' can indirectly influence 'the distance travelled' by the drug shipment. If 'the temperature excursion tolerance level of the drug' is very small (strictly between +/- 2 degree Celsius), then the shipper might use a distribution circuit which is extremely safe. For example, connecting hubs with have good infrastructure, trained equipment operator, less tarmac waiting time etc. And the selection of different distribution circuit can effect the actual distance travelled by the shipment. If 'the temperature excursion tolerance level of the drug' is very large (+/- 15 degree Celsius), then the shipper might use a normal distribution circuit.	FREIGHT FORWARDER (I)
			'The distance travelled by the shipment' cannot change 'the temperature excursion tolerance level of the drug'.	

4-8	Selection of distribution circuit	SINGLE DIRECT EFFECT (V)	'The temperature excursion tolerance level of the drug' can influence 'the distribution circuit selected by the shipper'. If 'the temperature excursion tolerance level of the drug' is very small (strictly between +/- 2 degree Celsius), then the shipper might use a distribution circuit which is extremely safe. For example, connecting hubs with have good infrastructure, trained equipment operator, less tarmac waiting time etc., But if the 'the temperature excursion tolerance level of the drug' is very large (+/- 15 degree Celsius), then the shipper might use a normal distribution circuit.	FREIGHT FORWARDER (I)
			'The distribution circuit selected by the shipper' cannot change 'the temperature excursion tolerance level of the drug'.	
4-9	Cost of packaging (Active vs. Passive system)	SINGLE EFFECT (V)	'the temperature excursion tolerance level of the drug' can influence' the cost of packaging' (selection between active vs. passive packaging system). If the temperature excursion tolerance level is too small, then the shipper will use an active packaging system which may be very expensive. But if the temperature excursion tolerance level is high, the shipper may use a passive packaging system that is inexpensive. The temperature excursion tolerance level was one of the top factors considered by the drug manufacturer in the decision making process.	DRUG MANUFACTURER
			'Cost of packaging system' (selection between active vs. passive) cannot change the 'the temperature excursion tolerance level of the drug'.	
4-10	Shipper's concern about the capacity of the packaging system to be flexible to unexpected ambient temperature	SINGLE EFFECT (V)	The temperature excursion tolerance level of the drug' can indirectly influence 'the shipper's concern about the capacity of the packaging system to change to unexpected ambient temperature'. If 'the temperature excursion tolerance level of the drug' is small (+/- 2 degree Celsius), then the shipper will be more concern about if the packaging system can cope with unexpected temperature profile.. But if 'the temperature excursion tolerance level of the drug' is high (+/- 20 degree Celsius) the shipper will be less concern about this feature of the packaging system.	FREIGHT FORWARDER (I)
			'Capacity of the packaging system to be change to unexpected ambient temperature' cannot change "the temperature excursion tolerance level of the drug'	
4-11	Shipper's concern about the supervision and maintenance requirement during transportation	SINGLE EFFECT (V)	The freight forwarder mentioned that all temperature-controlled shipments require constant supervision.	FREIGHT FORWARDER (I)
			'The supervision and maintenance requirement of a packaging system during transportation' cannot 'the temperature excursion tolerance level of the drug'.	
4-12	Shipper's concern about the reliable functioning of the packaging system during transportation	SINGLE EFFECT (V)	If 'the temperature excursion tolerance level of the drug' is small, the shipper will be more 'concern about the reliable functioning of the packaging system'.	FREIGHT FORWARDER (I)
			'The concern about the reliable functioning of the packaging system' cannot change "temperature excursion tolerance level of the drug'.	

5	Shipper's concern about the temperature profile of the origin and destination country			Source
5-6	Time to market	NO EFFECT (O)	'The shipper's concern about the temperature profile of the origin and destination country' will not influence the drug manufacturer's urgency to being the product to the market on time (time to market).	FREIGHT FORWARDER (I)
			The drug manufacturer's urgency to being the product to the market on time (time to market) will not influence 'the shipper's concern about the temperature profile of the origin and destination country'.	
5-7	Distance to be travelled	SINGLE EFFECT (V)	The shipper's concern about the temperature profile of the origin and destination country' can indirectly influence 'the distance travelled'. This is because the shipper might use a different distribution circuit that is quick or safer, and this can influence the actual distance travelled by the shipment.	FREIGHT FORWARDER (I)
			'The distance travelled by the drug shipment' will not influence 'the shipper's concern about the temperature profile of the origin and destination country'.	
5-8	Selection of distribution circuit	SINGLE EFFECT (V)	'The shipper's concern about the temperature profile of the origin and destination country' can influence the decision in 'selecting a particular distribution circuit'.	FREIGHT FORWARDER (I)
			'The distribution circuit selected' cannot influence 'the shipper's concern about the temperature profile of the country of origin and destination'. This factor is considered before finalizing the distribution circuit.	
5-9	Cost of packaging (Active vs. Passive system)	SINGLE EFFECT (V)	'The shipper's concern about the temperature profile of the origin and destination country' can influence the shipper to use a particular packaging system which may increase or decrease 'the cost of packaging'.	FREIGHT FORWARDER (I)
			The selection of a packaging system is taken based on the temperature profile of the country of origin and destination. This means that temperature is studied first before selection of the packaging system, not the opposite. So that 'the cost of packaging' cannot influence 'the shipper's concern about the temperature profile of the country of origin and destination'.	
5-10	Shipper's concern about the capacity of the packaging system to be flexible to unexpected ambient temperature	SINGLE EFFECT (V)	'The shipper's concern about the temperature profile of the origin and destination country' can indirectly influence 'the shipper's concern about the capacity of the packaging system to be flexibility to the unexpected ambient temperature'. If the shipper feels that the temperature profile of these countries are uncertain, then the shipper will be more concern about this feature.	FREIGHT FORWARDER (I)
			'The shipper's concern about the capacity of the packaging system to be flexible to the unexpected ambient temperature' cannot influence 'the shipper's concern about the temperature profile of the country of origin and destination'.	

5-11	Shipper's concern about the supervision and maintenance requirement during transportation	SINGLE EFFECT (V)	'The shipper's concern about the temperature profile of the origin and destination country' can indirectly influence 'the shipper's concern about the supervision and maintenance required during transportation'. If the temperature profile of these countries are facing extreme climate, then the shipper may used a particular packaging system (mostly an active packaging system) that may need increased supervision and maintenance during transportation.	FREIGHT FORWARDER (I)
			'The shipper's concern about the maintenance and supervision required during transportation' cannot change 'the shipper's concern about the temperature profile of the origin and destination country'.	
5-12	Shipper's concern about the reliable functioning of the packaging system during transportation	SINGLE EFFECT (V)	'The shipper's concern about the temperature profile of the origin and destination country' can indirect influence 'the shipper's concern about the reliable functioning of the packaging system during transportation'. If the temperature in these countries are extreme (bad temperature profile), then this may concern the shipper about he well functioning of these packaging system.	FREIGHT FORWARDER (I)
			'The shipper's concern about the reliable functioning of the packaging system' cannot change 'shipper's concern about the temperature profile of the origin and destination country'.	

6	**Time to market**			**Source**
6-7	Distance to be travelled	SINGLE EFFECT (V)	As per the freight forwarder, the drug manufacturer's urgency to bring a drug to the market on time ('time to market') can influence the shipper to choose different distribution circuit (routes) that may indirectly increase or decrease the actual distance travelled.	FREIGHT FORWARDER (I)
			'The distance travelled by the drug shipment' cannot influence the drug manufacturer's urgency to bring the product to the market on time ('time to market')	
6-8	Selection of distribution circuit	SINGLE EFFECT (V)	As per the freight forwarder, the drug manufacturer's urgency to bring a drug to the market on time ('time to market') can influence 'the shipper choose different distribution circuit' that is extremely safe.	FREIGHT FORWARDER (I)
			'The distribution circuit selected by the shipper' cannot influence 'the drug manufacturer's urgency to bring the product to the market' (time to market).	
6-9	Cost of packaging (Active vs. Passive system)	SINGLE EFFECT (V)	The drug manufacturer's urgency to bring a drug to the market on time' can influence the shipper's decision to choose a particular packaging system (active vs. passive), and this may increase/decrease 'the cost of packaging'. The freight forwarder has faced several situation where the drug manufacturer requested for expensive packaging container in such situations.	FREIGHT FORWARDER (I)
			'The cost of packaging system' (selection between active vs. passive) cannot influence 'the drug manufacturer's urgency to bring the product to the market on time'.	

6-10	Shipper's concern about the capacity of the packaging system to be flexible to unexpected ambient temperature	NO EFFECT (O)	'The drug manufacturer's urgency to bring a drug to the market on time' cannot influence' the shipper's concern about the capacity of the packaging system to cope its thermal temperature to unexpected ambient temperature'.	FREIGHT FORWARDER (I)
			'The shipper's concern about the capacity of the packaging system to cope with the unexpected ambient temperature' cannot influence 'the drug manufacturer's urgency to bring a drug to the market on time'.	
6-11	Shipper's concern about the supervision and maintenance requirement during transportation	SINGLE EFFECT (V)	'The drug manufacturer's urgency to bring a drug to the market on time' can influence 'the shipper's concern about supervision and maintenance requirement during transportation'. Since these shipments are high priority shipment, therefore more supervision and care is given.	FREIGHT FORWARDER (I)
			'The shipper's concern about supervision and maintenance requirement during transportation' cannot influence 'the shipper's urgency to bring the product to the market on time'.	
6-12	Shipper's concern about the reliable functioning of the packaging system during transportation	SINGLE EFFECT (V)	'The drug manufacturer's urgency to bring a drug to the market on time' can influence 'the shipper's concern about the reliable functioning of the packaging system during transportation'. Since these are high priority shipments, the shipper will be more 'concern about the well functioning of the packaging system'.	FREIGHT FORWARDER (I)
			'The shipper's concern about the reliable functioning of the packaging system' cannot influence 'the drug manufacturer's urgency to bring the drug to the market on time'.	

7	**Distance to be travelled**			**Source**
7-8	Selection of distribution circuit	MULTIPLE EFFECT (X)	The distance between the country of origin and destination' can compel shipper to use different distribution networks to reach the final destination. The longer the distance, the more options the shipper has to use different distribution circuits based on several factors such as safety, speed, cost consideration etc..	FREIGHT FORWARDER (I)
			'The distribution circuit selected by the shipper' can increase/ decrease 'the actual distance travelled by the drug shipment'.	
7-9	Cost of packaging (Active vs. Passive system)	SINGLE EFFECT (V)	'The distance of the journey' has a direct effect 'the cost of packaging'. If the distance to be travelled is long, the shipper may consider using an active packaging system because it got longer transport life. This will increase the shipper's cost of packaging. On the other hand, if the distance is short, the shipper may use a passive packaging system that has lesser transport life. But this will reduce 'the cost of the packaging'. During the interview, the drug manufacturer has also mentioned that they use different packaging solutions for domestic and international shipments, and distance is an important factor.	MANUFACTURER

			The drug manufacturer has clearly stated that a choice between a packaging system (cost of packaging) will not change 'the distribution circuit' or' the distance'. It is because 'the distribution circuit' and 'the distance to be travelled' is decided before the selection of the packaging system.	DRUG
7-10	Shipper's concern about the capacity of the packaging system to be flexible to unexpected ambient temperature	SINGLE EFFECT (V)	The actual of the distance travelled by the drug shipment' can influence 'the shipper's concern about the capacity of the packaging system to cope to unexpected ambient temperature'.	FREIGHT FORWARDER (I)
			The shipper's concern about the capacity of the packaging system to cope to unexpected ambient temperature' cannot change 'the actual distance travelled by the shipment'.	
7-11	Shipper's concern about the supervision and maintenance requirement during transportation	MULTIPLE EFFECT (X)	Supervision and maintenance is only possible if trained operators are available at each connecting hub. So the selection of the right distribution circuit is important. Since distance is closely linked with the distribution circuit, it is related.	FREIGHT FORWARDER (I)
			'The shipper concern about the supervision and maintenance required during transportation' can influence 'to choose a distribution circuit' that may increase/ decrease 'the actual distance travelled'.	
7-12	Shipper's concern about the reliable functioning of the packaging system during transportation	MULTIPLE EFFECT (X)	'The distance travelled by the drug shipment' can influence 'the shipper's concern about the reliable functioning of the packaging decision during transportation'. The shipper will be more concern about this factor if the distance to be travelled is longer, and will be less concern about this factor if the distance to be travelled is short.	FREIGHT FORWARDER (I)
			'The shipper's concern about the reliable functioning of the packaging system' can influence the shipper's decision to choose a safer distribution circuit that will indirectly increase or decrease 'the distance to be travelled'.	

8	**Selection of distribution circuit**			**Source**
8-9	Cost of packaging (Active vs. Passive system)	SINGLE EFFECT (V)	'The distribution circuit' can influence the shipper's decision on the type of packaging container to be used. If the distribution circuit is a safe route, the shipper may consider a passive packaging system but if the distribution circuit is complex, then the shipper may use an active packaging system. This may increase or decrease 'the cost of packaging'.	DRUG MANUFACTURER
			'The cost of packaging' (selection between an active Vs. passive system) cannot influence 'the selection of the distribution circuit'.	
8-10	Shipper's concern about the capacity of the packaging system to be flexible to unexpected ambient temperature	SINGLE EFFECT (V)	'The selection of distribution circuit' can influence 'the shipper's concern about the capacity of the packaging system to be flexible to the unexpected ambient temperature'. Some connecting hubs may in countries with extreme weather so this can make the shipper more concern about this feature.	FREIGHT FORWARDER (I)
			'The shipper's concern about the capacity of the packaging system to cope with unexpected ambient temperature' cannot influence 'the selection of distribution circuit'.	

8-11	Shipper's concern about the supervision and maintenance requirement during transportation	MULTIPLE EFFECT (X)	The selection of distribution circuit' can influence 'the shipper's concern about the supervision and maintenance required during the transportation'. Different connecting hubs may or may not have operational staffs to do the necessary supervision and maintenance. So it can effect the level of supervision required.	FREIGHT FORWARDER (I)
			'The shipper's concern about the maintenance and supervision required during the transportation' can influence 'the shipper's decision to choose a distribution circuit'.	
8-12	Shipper's concern about the reliable functioning of the packaging system during transportation	MULTIPLE EFFECT (X)	'The selection of distribution circuit' can influence 'the shipper's concern about the reliable functioning of the packaging system during transportation'. Different connecting hubs may have its own advantages and disadvantage. The freight forwarder mentioned that they experienced situation where some connecting hubs did not have necessary power socket for charging their active packaging containers. So they were unable to recharge the battery of their active packaging containers.	DRUG MANUFACTURER & FREIGHT FORWARDER (I)
			'The shipper's concern about the reliable functioning of the packaging system' can influence the shipper to choose a safer 'distribution circuit'.	

9	**Cost of packaging (Active vs. Passive system)**			**Source**
9-10	Shipper's concern about the capacity of the packaging system to be flexible to unexpected ambient temperature	SINGLE EFFECT (A)	The cost of packaging' is the ultimate decision in the choosing a packaging decision. So it cannot influence 'the shipper's concern about the capacity of the packaging system to cope with unexpected ambient temperature'.	FREIGHT FORWARDER (I)
			'The shipper's concern about the capacity of the packaging system to cope to unexpected ambient temperature' can influence the decision in choosing a particular packaging system (Active Vs. Passive), hence 'the cost of packaging'.	
9-11	Shipper's concern about the supervision and maintenance requirement during transportation	SINGLE EFFECT (A)	'The cost of packaging' is the ultimate decision in the choosing a packaging decision. So it cannot influence' the shipper's concern about the supervision and maintenance requirement during transportation'.	FREIGHT FORWARDER (I)
			'The shipper's concern about the supervision and maintenance required during transportation' can influence the shipper to choose a particular packaging system. If the shipper does not have the necessary staff for constant supervision and maintenance along the distribution circuit, then he/she would prefer a passive packaging system instead of active packaging system. This can change the 'cost of packaging'.	

9-12	Shipper's concern about the reliable functioning of the packaging system during transportation	SINGLE EFFECT (A)	'The cost of packaging' is the ultimate decision in the choosing a packaging decision. So it cannot influence' the shipper's concern about the reliable functioning of the packaging system'. This concern (factor) is thought before finalizing a packaging decision, not after.	FREIGHT FORWARDER (I)
			'The shipper's concern about the reliable functioning of the packaging system' can influence the shipper's decision to choose a particular packaging system. This can increase or decrease 'the cost of packaging'.	

10	**Shipper's concern about the capacity of the packaging system to be flexible to unexpected ambient temperature**			**Source**
10-11	Shipper's concern about the supervision and maintenance requirement during transportation	NO EFFECT (O)	'The shipper's concern about the capacity of the packaging container to be flexible to the unexpected ambient temperature' will not influence 'the shipper's concern about the supervision and maintenance requirement during transportation'. There is no relation between them.	FREIGHT FORWARDER (I)
			'Shipper's concern about the supervision and maintenance of the packaging system during transportation' cannot influence 'the shipper's concern about the capacity of the packaging system to be flexible to unexpected temperature'. This is because the thermal setting in an active container are automated and do not require human intervention.	

10-12	Shipper's concern about the reliable functioning of the packaging system during transportation	NO EFFECT (O)	'The shipper's concern about the capacity of the packaging system to cope with the unexpected ambient temperature' has no connection with 'the shipper's concern about the reliable functioning of the packaging system'.	FREIGHT FORWARDER (I)
			'The shipper's concern about the reliable functioning of the packaging system' cannot influence 'the shipper's concern about the capacity of the packaging system to cope with the unexpected ambient temperature'.	

11	**Shipper's concern about the supervision and maintenance requirement during transportation**			**Source**
11-12	Shipper's concern about the reliable functioning of the packaging system during transportation	MULTIPLE EFFECT (X)	'Shipper's concern about the supervision and maintenance of the packaging system required during transportation' can influence' the shipper's concern for the reliable functioning of the packaging system'.	FREIGHT FORWARDER (I)
			The shipper's concern about the reliable functioning of the packaging system can influence the concern for constant supervision and maintenance required during transportation.	

From the SSIM, the relationship among factors will be transformed into a binary matrix called the '**Reachability matrix',** which is shown in Figure 12. The relationship among factors is translated into binary numbers as follows: (Govindan et al., 2012)

- If the (i, j) entry in the SSIM is V, then the (i, j) entry in the reachability matrix becomes 1 and the (j, i) entry becomes 0.
- If the (i, j) entry in the SSIM is A, then the (i, j) entry in the reachability matrix becomes 0 and the (j, i) entry becomes 1.
- If the (i, j) entry in the SSIM is X, then the (i, j) entry in the reachability matrix becomes 1 and the (j, i) entry also becomes 1.
- If the (i, j) entry in the SSIM is O, then the (i, j) entry in the reachability matrix becomes 0 and the (j, i) entry also becomes 0.

In the **Level Partition Iteration**, there are two sets which are a) reachability set and b) antecedent set. "The reachability set consists of factors itself and the other factors that it many impact, whereas the antecedent set consists of the factors itself and the other factor that may impact it" (Attri, Dev, & Sharma, 2013, p. 5). This can be better explained with a simple example as follows:

In Figure 13, row 1 of the Level Partition Iteration lays Element 1. The reachability set on row 1 includes all the elements that element 1 can impact or influence. This means element 1 can influence element no. 1,7,8,9,11 and 12. The antecedent set includes all the elements that can impact or influence element 1. This means element 1 can get influenced by elements 1 & 2.

REACHABILITY MATRIX

		1	2	3	4	5	6	7	8	9	10	11	12		
	Decisive factors in choosing packaging system	Size and weight of the drug shipment	Product type	Temperature range of the drug	Temperature excursion tolerance level	Shipper's concern about the temperature profile of the origin and destination country	Time to market	Distance to be travelled	The distribution circuit	Packaging cost	Shipper's concern about the capacity of the packaging system to be flexible to unexpected ambient temperature	Shipper's concern about the supervision and maintenance requirement during transportation	Shipper's concern about the reliable functioning of the packaging system during transportation	DRIVING POWER	RANK
1	Size and weight of the drug shipment	1	0	0	0	0	0	1	1	1	0	1	1	6	IV
2	Product type	1	1	1	1	1	0	1	1	1	1	1	1	11	I
3	Temperature range of the drug	0	0	1	0	1	0	1	1	1	1	1	1	8	II
4	Temperature excursion tolerance level	0	0	0	1	1	0	1	1	1	1	1	1	8	II
5	Shipper's concern about the temperature profile of the origin and destination country	0	0	0	0	1	0	1	1	1	1	1	1	7	III
6	Time to market	0	0	0	0	0	1	1	1	1	1	1	1	7	III
7	Distance to be travelled	0	0	0	0	0	0	1	1	1	1	1	1	6	IV
8	The distribution circuit	0	0	0	0	0	0	1	1	1	1	1	1	6	IV
9	Packaging cost	0	0	0	0	0	0	0	0	1	0	0	0	1	VI
10	Shipper's concern about the capacity of the packaging system to be flexible to unexpected ambient temperature	0	0	0	0	0	0	0	0	1	1	0	0	2	VI
11	Shipper's concern about the supervision and maintenance requirement during transportation	0	0	0	0	0	0	1	1	1	0	1	1	5	V
12	Shipper's concern about the reliable functioning of the packaging system during transportation	0	0	0	0	0	0	1	1	1	0	1	1	5	V
	DEPENDENCE POWER	2	1	2	2	4	1	10	10	12	8	10	10		
	RANK	V	VI	V	V	IV	VI	II	II	I	III	II	II		

Figure 12 - Reachability Matrix

Figure 13 - Level Partition Iteration

LEVEL PARTITION ITERATION

Partition of reachability matrix : Interaction 1

Element No.	Reachability set	Antecedent set	Intersection	Level
1	1,7,8,9,11,12	1,2	1	
2	1,2,3,4,5,7,8,9,10,11,12	2	2	
3	3,5,7,8,9,10,11,12	2,3	3	
4	4,5,7,8,9,10,11,12	4,2	4	
5	5,7,8,9,10,11,12	2,3,4,5	5	
6	6,7,8,9,10,11,12	6	6	
7	7,8,9,10,11,12	1,2,3,4,5,6,7,8,11,12	7,8,11,12	
8	7,8,9,10,11,12	1,2,3,4,5,6,7,8,11,12	7,8,11,12	
9	9	1,2,3,4,5,6,7,8,9,10,11,12	9	1
10	9,10	2,3,4,5,6,7,8,10	10	
11	7,8,9,10,11,12	1,2,3,4,5,6,7,8,11,12	7,8,11,12	
12	7,8,9,11,12	1,2,3,4,5,6,7,8,11,12	7,8,11,12	

Partition of reachability matrix : Interaction 2

Eliminated element 9

Element No.	Reachability set	Antecedent set	Intersection	Level
1	1,7,8,11,12	1,2	1	
2	1,2,3,4,5,7,8,10,11,12	2	2	
3	3,5,7,8,10,11,12	2,3	3	
4	4,5,7,8,10,11,12	4,2	4	
5	5,7,8,10,11,12	2,3,4,5	5	
6	6,7,8,10,11,12	6	6	
7	7,8,10,11,12	1,2,3,4,5,6,7,8,11,12	7,8,11,12	
8	7,8,10,11,12	1,2,3,4,5,6,7,8,11,12	7,8,11,12	
10	10	2,3,4,5,6,7,8,10	10	2
11	7,8,10,11,12	1,2,3,4,5,6,7,8,11,12	7,8,11,12	
12	7,8,11,12	1,2,3,4,5,6,7,8,11,12	7,8,11,12	

Partition of reachability matrix : Interaction 3

Eliminated element 10

Element No.	Reachability set	Antecedent set	Intersection	Level
1	1,7,8,11,12	1,2	1	
2	1,2,3,4,5,7,8,11,12	2	2	
3	3,5,7,8,11,12	2,3	3	
4	4,5,7,8,11,12	4,2	4	
5	5,7,8,11,12	2,3,4,5	5	
6	6,7,8,11,12	6	6	
7	7,8,11,12	1,2,3,4,5,6,7,8,11,12	7,8,11,12	3
8	7,8,11,12	1,2,3,4,5,6,7,8,11,12	7,8,11,12	3
11	7,8,11,12	1,2,3,4,5,6,7,8,11,12	7,8,11,12	3
12	7,8,11,12	1,2,3,4,5,6,7,8,11,12	7,8,11,12	3

Partition of reachability matrix : Interaction 4

Eliminated element 7,8,11 & 12

Element No.	Reachability set	Antecedent set	Intersection	Level
1	1	1,2	1	
2	1,2,3,4,5	2	2	
3	3,5	2,3	3	
4	4,5	4,2	4	
5	5	2,3,4,5	5	4
6	6	6	6	

Partition of reachability matrix : Interaction 4

Eliminated element 5

Element No.	Reachability set	Antecedent set	Intersection	Level
1	1	1,2	1	5
2	1,2,3,4	2	2	
3	3	2,3	3	5
4	4	4,2	4	5
6	6	6	6	

Partition of reachability matrix : Interaction 4

Eliminated element 1,3,4

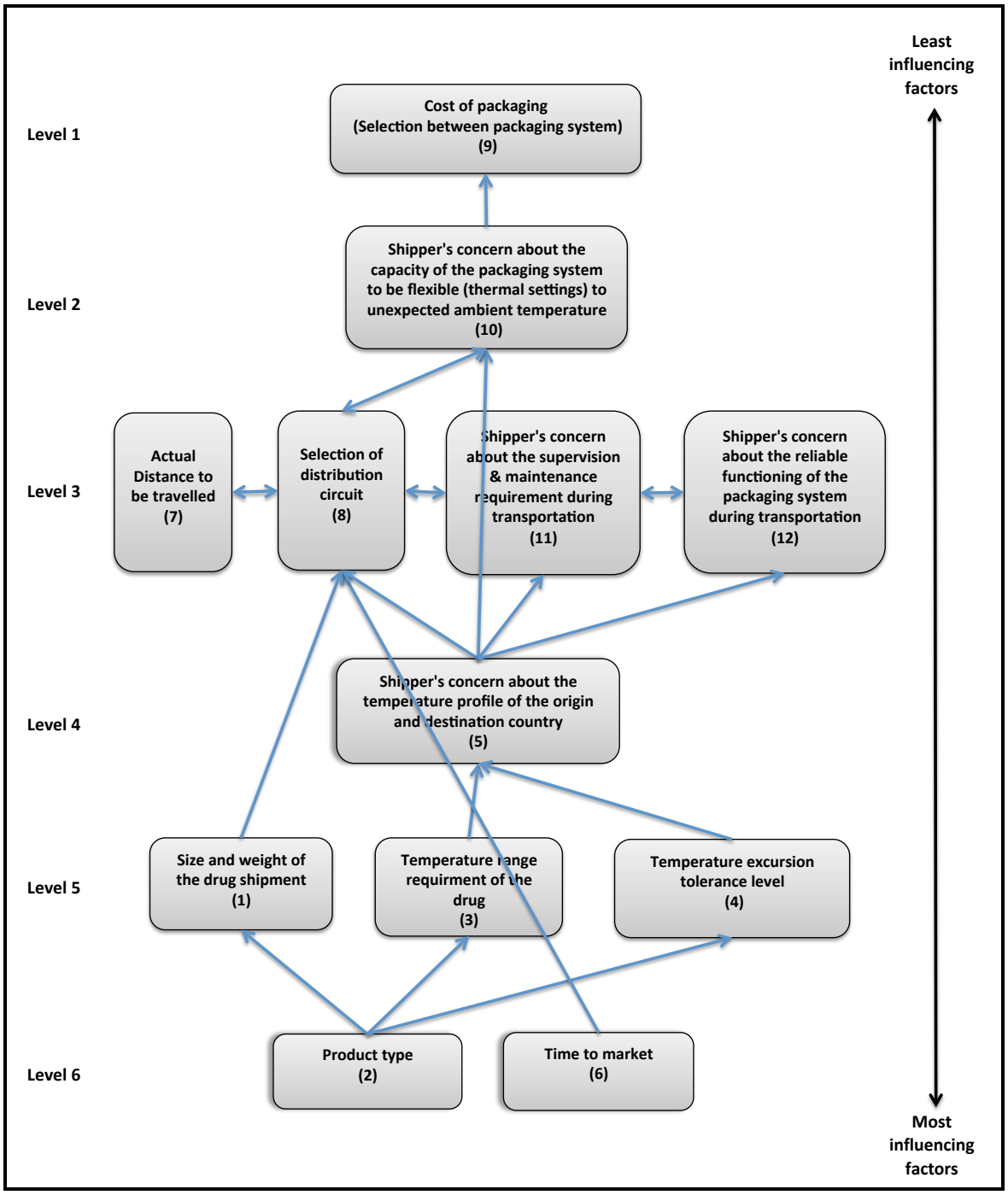
Element No.	Reachability set	Antecedent set	Intersection	Level
2	2	2	2	6
6	6	6	6	6

5. DISCUSSION OF THE RESULTS

ISM Diagram

After the interview with the Drug manufacturer, Freight forwarder 1 and Freight Forwarder 2 (validation purpose only), all the cells of the SSIM were filled and the below ISM diagram was generated.

Figure 14 - Final ISM Diagram



The factors in the diagram are divided into **six levels** based on the manager's flow of decision-making. The factors considered by the manager at the initial stage of the decision-making process are placed at the bottom of the ISM diagram (highest being Level 6). These are considered to be the most influential factors. The factors that are considered in the last stage of the decision-making process are placed at the top of the ISM diagram (lowest being Level 1). As mentioned earlier, the ISM diagram communicates the result to the user in the combination of words and diagram (James, 1988). This diagram shows the flow of the decision-making process that is supposed to be followed. It shows how one factor influences the other factor(s).

Level 6

At the bottom-most level of the ISM diagram lays the most important factors a manager would consider at the initial stage of a cold chain packaging decision-making process. Among them are: a) 'Product type of the drug' and b) 'Time to Market'.

'Product type' is placed at the highest influential level in the ISM Diagram because of its influence on the other factors such as 'Temperature range requirement of the drug' (3), 'Temperature excursion tolerance level' (4) and 'Size of the drug shipment' (1). The 'product type' is capable of influencing other factors beyond Level 5, as it can extend until Level 1. The other reason for its placement at this level (Level 6) is because there is no other factor that could influence the 'product type' (2). So this should be the key factor to consider at the early stage of the decision making process.

Initially, it was the drug manufacturer who recommended to include 'Product type' as part of the study. It was mentioned that drug products are labeled under different types such as 'vaccines', 'bio-similar', 'biologics', 'oncology', 'narcotics' etc.. These 'product types' were the primary information used for creating a SOP (Standard Operating Procedure) among the different cold chain partners.

During our interview with the Freight Forwarder 1, we learned that many players in the cold chain (including the freight forwarders) had a tendency to generalize the care and attention required for a particular drug shipment depending on 'the product type' specified on the label of these container. This is because they know that certain product types require more or less attention. For example, product types such as 'bio-similar' and 'biologics drugs' have stricter temperature range requirements compared to other medical products. So they are given extra care.

The Freight Forwarder 2 (Independent participant for validation purpose) also agreed with the placement of this factor at this level. They confirmed how 'product type' could influence the temperature requirements of the drug (Factor 3 & 4), and the 'size of the drug shipment' (1) at Level 5. They narrated the following two empirical examples to validate their opinion:

a) On rare occasions, the freight forwarders receive shipments of delicate chemicals known as 'Isotopes'. The main challenge in transporting such product type is its unique characteristics where the chemical will deplete itself in time. For example, the chemical will reduce its size within a certain time period. Some of these products can even increase their rate of depletion if it is exposed to unacceptable temperature (Factor 3 & 4). It was a challenging task for the freight forwarder to transport this product due to the special characteristics of this chemical. Therefore special primary, secondary and tertiary packaging was required for such a product. This extra level of packaging indirectly influences the overall 'size of the drug shipment' (1). This confirms the interrelation between the 'product type' (2) at Level 6 to the temperature related factor (3 & 4) and 'size and weight of the drug shipment' (1).

b) Regulations as per IATA (The International Air Transport Association) require that each product have to be assigned a product code. Temperature-sensitive healthcare product has its own code, and a special guidelines must be followed fall under 'IATA's Chapter 17 – Temperature Control Regulation'. Conforming to

such stringent guidelines can impact the entire decision-making process. So ‘product type’ is well placed at Level 6.

Another factor placed at Level 6 is **‘Time to market’.** The type of packaging system to be selected is heavily dependent on factors such as ‘distance between the origin and destination country’ (7), and the ‘distribution circuit’ used (8). The drug manufacturer’s urgency to bring the product to the market as quickly as possible can force him/her to use an alternative ‘distribution circuit’ that is faster or even safer. ‘Time to market’ factor was recommended by the freight forwarder 1 who believed that this factor was one of the factors a manager should think about at the initial stage of the decision-making process because this can greatly impact the entire distribution process.

Large bio-pharmaceutical companies know all too well the pressures of getting their products to market at the right time. For example, The Canadian law grants a maximum of 20 years of patent protection to companies that develop new biologics drugs, this is a small window of time designed to allow developers (drug manufacturers) of breakthrough medicines to make a fair commercial return on their heavy investment. (PwC, 2014). But as soon as the patent period is over, biosimilar manufacturers (generic version) try to enter the market as soon as possible. Biosimiliars are cost effective alternative to the high priced branded biologics, offering cost advantages to both payers and patients (BlackStone, 2012). So generic drug manufacturers are in fierce competition to bring the biosimilar to the market as soon as the biologic drug’s patent expires.

The freight forwarder 1 illustrated this concept with a real life situation about one of their client, a biosimilar manufacturer, who was anxiously waiting for a particular biologics drugs’ patent expiration date, in order to bring their new biosimilar product to the market the very next day. If the product fails to enter the market on time, there can be severe consequences. At least, they can miss a significant sales opportunity. In the worst case, the drug may not find an active market at all. The bio-similar drug manufacturer wanted to bring the drug from the warm climate

of India and the destination was Canada. Considering the various factors such as ‘size and weight of the shipment’, ‘distance to be travelled’, ‘distribution circuit’, ‘temperature requirements’ etc., the freight forwarder 1 suggested a passive packaging system to the drug manufacturer keeping the cost consideration in mind. The only drawback of using a passive packaging system was that it had to go through a designing and internal quality testing process that would consume several days or months. This approved passive packaging system was supposed to be sent to their supplier in Asia. But since the drug manufacturer was very concerned about the ‘Time to market’ factor, the drug manufacturer decided to override the suggestion of their freight forwarder and choose an active packaging system instead. The drug manufacturer had to bear almost an extra cost of CAD $ 30,000 for changing the type of packaging system (active over passive system). They also demanded excess supervision during the entire distribution process. The best distribution circuits were selected considering the potential risk to the packaging container. The drug manufacturer’s reasons to choose an active packaging system were as follows:

i) Quick Availability – Active packaging container was not custom made, it was available all around the world. So there was no time delay (no need to design and test the passive packaging system).

ii) Concern about the temperature profile of the country of origin - The drug manufacturer was very much concerned with the warm and humid climate in the country of origin. Even though the freight forwarder assured a safe distribution of the shipment, the drug manufacturer did not want to take any risk, and decided to use an active packaging system instead.

However, the freight forwarder felt that it was a wiser choice for the drug manufacturer to achieve their long-term strategic goals. The above example shows how ‘Time to factor’ (6) at Level 6 can influence all the factors at Level 3 and above.

The freight forwarder 2 (Independent participant for validation purpose) has validated the placement of this factor with another example. When Nestle Group

wanted to introduce a new brand of bottled water to the market, they had a deadline to meet. Due to this urgency, Nestle Company asked the freight forwarder to transport these containers of bottled water using airplanes, in spite of the excess cost. The participant mentioned that clients such as bio-similar manufacturer are in a very competitive industry so they often receive such demands and preferences. This reconfirms the placement of 'Time to market' (6) on Level 6.

Level 5

Once the drug manufacturer is clear about the 'product type' to be distributed and the degree of urgency to bring the product to the market on time, he/she will need more details about the product characteristics. The ISM methodology has placed three factors in the ISM Diagram at Level 5, which are a) 'size of the drug shipment' (1), b) 'temperature range of the drug' (3), and c) 'temperature excursion tolerance level' (4).

The 'size of the drug shipment' can have a big impact on the decision-making process. The freight forwarder 1 gave us a detailed explanation with the help of a PowerPoint presentation about how the 'size of the drug shipment' can influence the rest of the decision making process, especially the 'distribution circuit' selected. If the 'size of the drug shipment' is small, then it can easily be loaded in the cargo section of most passenger aircraft. But when the 'size of the drug shipment' is large, ordinary passenger aircraft may not have the space (capacity) to accommodate them. Since these shipments are temperature-sensitive items packed in containers with limited transport life, the freight forwarder will be forced to use the next best alternative distribution route to send the drug to the final destination. So the 'size of the drug shipment' can influence 'distribution circuit' and indirectly increase or decrease 'distance travelled by the shipment'. The drug manufacturer also used 'size of the drug shipment' as one of the key factors in the early stage of the cold chain packaging decision-making process.

Another important factor the manager (drug manufacturer & freight forwarder) should consider will be *the temperature requirements of the particular drug shipment (Factor 3 & 4).* Even among a particular 'product type', there might be different sub-classes or types that may have minor differences in the temperature requirements. So at this stage, the drug manufacturer must collect more details about individual drug's characteristics. Depending on the temperature requirement of that particular drug shipment, the 'shipper's concern about the temperature profile of the country of origin and destination' (5) at Level 4 may increase or decrease. If the temperature requirement of the drug is very demanding, then it will force the shipper to be more concerned about the temperature profile of the countries the product is travelling through, and vice-versa.

In the case of vaccines, even within the 'vaccine' product type, there are many subdivisions known as 'classes'. Each class within the same product type has different temperature requirements. An example of classes of vaccines and their individual temperature requirement as per WHO is shown below:

Figure 15 - WHO classification and temperature criteria for international shipment of vaccines

WHO classification and temperature criteria for international shipment of vaccines (for at least 48 hours)

Class	Type of vaccine	Ambient temperature	Minimum temperature allowed	Maximum temperature allowed
A	OPV	+43°C	no limit	+8°C
B	BCG Hib (freeze-dried) measles MR MMR meningococcal A&C yellow fever	+43°C	no limit	+30°C
C	DTP DTP–HepB DTP–Hib (liquid) DT	+43°C	+2°C	+30°C
	IPV HepB Hib (liquid) Td TT	-5°C	+2°C	+30°C

Source: (WHO, 2005)

Below are the definitions given by WHO about these individual packaging classification:

Class A Packaging

"The vaccine must be packed to ensure that the warmest temperature inside the insulated package does not rise above +8°C in continuous outside ambient temperatures of +43°C for a period of at least 48 hours" (WHO, 2005, p. 1).

Class B Packaging

"The vaccines must be packed to ensure that the warmest temperature inside the insulated package does not rise above +30°C in continuous outside ambient temperatures of +43°C for a period of at least 48 hours" (WHO, 2005, p. 1).

Class C Packaging

"The vaccines must be packed to ensure that:

• the warmest temperature inside the insulated package does not rise above +30°C in continuous outside ambient temperatures of +43°C for a period of at least 48 hours; and

• the coolest storage temperature of the vaccine does not fall below +2°C in continuous external temperatures of -5°C for a period of at least 48 hours". (WHO, 2005, p. 2).

Level 4

If the temperature requirement factors at Level 5 are very demanding, it will influence 'the shipper's concern about the temperature profile of the country of origin and destination' at Level 4. This is one of the levels that changes the distribution process from an ordinary supply chain to a temperature-sensitive supply chain (i.e. cold chain). From this level onwards, the shipper's attention will be to maintain a controlled-temperature environment throughout the distribution process. But the shipper cannot just select a cold chain packaging system without understanding the temperature profile of the country of origin and country of destination. The importance of the shipper's concern about this level can be easily understood with the example explained at Level 6 where the drug manufacturer decided to use an active packaging system in spite of the freight forwarder's recommendation to use a passive packaging system. This was because of the shipper's extra concern about the warm climate in the country of origin.

Level 3

Once the shipper has clearly understood the temperature requirement of the drug shipment at Level 5, and has also understood 'the temperature profile of the country of origin and destination' at Level 6, then the next step will be to plan a distribution circuit that matches to the criteria at Level 6, 5, 4 and also 3 itself. So the ISM diagram has placed four decisive factors equally at Level 3, which are a) 'distribution circuit used for transportation', b) 'distance to be travelled by the drug shipment' and c) 'shipper's concern about the supervision and maintenance

required during transportation' d) 'shipper's concern about the reliable functioning of the packaging system during transportation'. The reason that these four factors are placed equally at the same level of the ISM Diagram (Level 3) is because they all influence each other.

Firstly, the shipper has to determine the actual 'distance between country of origin and country of destination'. Distance will play an important role in the decision-making. The distribution process within the same country or a city closer to the neighboring country is different from a distribution process to a country in another continent. During our interview with the drug manufacturer, it was mentioned that for domestic transportation they preferred refrigerated trucks. But a well-planned cold chain packaging decision-making was necessary for international shipments.

Depending on the distance between the two countries, an ideal 'distribution circuit' has to be selected. But before considering a distribution circuit, the manager has to understand the options available to the shipper to perform 'constant supervision and maintenance of the packaging system during its journey'. For example, some connecting hubs (airports) may not have the trained operators to perform constant supervision and maintenance when required. Therefore, the manager has to consider a distribution circuit depending on the availability of these trained operators for supervision and maintenance. So 'shipper's concern about the supervision and maintenance requirement during transportation' (11) can directly influence the selection of the 'distribution circuit' (8) in the same level.

Another factor that is closely connected with the selection of the 'distribution circuit' (8) is the 'shipper's concern about the reliable functioning of the packaging during transportation' (12). The manager has to choose a distribution circuit considering the safety of the packaging system. Some connecting hubs in certain countries may have longer waiting time on the tarmac area, some may not have a separate cold chain storage area for temperature controlled product, or some countries will be facing an extreme weather at that point of time. So the manager has to consider all these complications before finalizing the distribution circuit.

During our interview with the freight forwarder 1, it was mentioned that some connecting hubs (airports) did not have the adequate power sockets for recharging the active packaging containers. So these packaging systems were transported for the rest of their journey without thermal cooling. This hampered the well functioning of these packaging systems.

Another time, the freight forwarder 1 experienced a situation where the active containers that were run on lithium batteries were parked on the airport's tarmac area for more than 3 hours when the ambient temperature was -40 degree Celsius. This caused a huge risk for the well-functioning of the active packaging system because sometimes the mechanics of this machine can stop functioning if the battery is exposed to extreme cold. The freight forwarder mentioned that certain airports have longer waiting times than others.

So all factors (7), (8), (11) and (12) at Level 3 influence each other, and it is the manager who will select a distribution circuit based on the other factors in the same level.

Level 2

At this stage, the shipper has finalized the distribution routes based on the factors on the Level 6 through Level 3. But before making the final decision on the selection of the packaging system (active vs. passive), the shipper has an option to consider the need to have a packaging system that can be flexible to the meet unexpected ambient temperature (10). Sometimes in spite of all this planning, the weather can be unpredictable, or waiting time in airports can extend without prior notice etc. So at this stage, the manager has an option to decide if he/she needs to consider selecting a packaging system that can withstand these unexpected situations.

Active packaging containers have the capability to cope with the unexpected temperature profile because its internal thermal setting is constant in spite of the

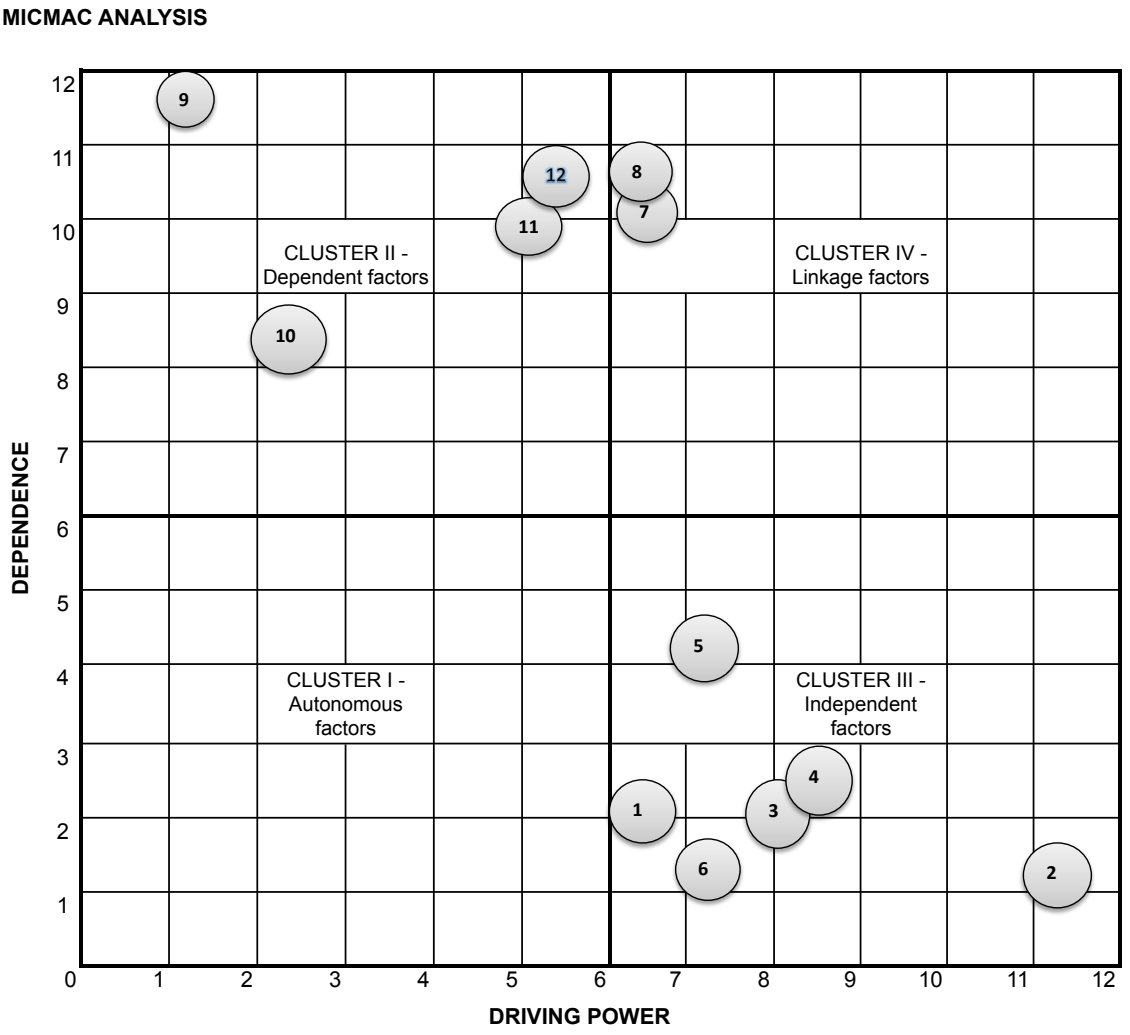
variance in the ambient temperature. The reason why ISM diagram has placed this factor at Level 2 is because the shipper can only think of this option if the distribution circuit is already selected. **The drug manufacturer has clearly mentioned that distribution circuit was finalized before choosing between the packaging systems.** So this factor plays a role at this stage of the decision making process.

At Level 1, the managers take the final decision on what type of packaging system should be finally selected considering all the factors below Level 1. The 'costs of packaging' is directly dependent on the type of packaging system selected. Active packaging systems are expensive compared to the passive packaging system. The freight forwarder has mentioned that an active packaging system is almost five times more expensive than a passive system. But companies choose them depending on the circumstances, and these circumstances are the factors from Level 1 through Level 6. At this stage, the manager can have maximum clarity on what type of packaging system has to be chosen.

MICMAC Analysis

An Interpretive Structural Modeling (ISM) methodology does not end with just an ISM diagram. It also includes a MICMAC Analysis. As mentioned in Section 3, the objective of the MICMAC analysis is to analyze the driving and dependence power of each factor (Govindan et al., 2010). It is only with the help of a MICMAC analysis that the ISM methodology will be complete. An ISM diagram only shows the flow of the decision-making process but a MICMAC analysis shows the individual characteristics of each factor.

Figure 16 - MICMAC Analysis



1 - Size and weight of the drug shipment
2 - Product type
3 - Temperature range requirement of the drug
4 - Temperature excursion tolerance level
5 - Shipper's concern about the temperature profile of the origin and destination country
6 - Time to market
7 - Distance to be travelled
8 - Selection of distribution circuit
9 - Packaging cost
10 - Shipper's concern about the capacity of the packaging system to be flexible to unexpected ambient temperature
11 - Shipper's concern about the supervision and maintenance requirement during transportation
12 - Shipper's concern about the reliable functioning of the packaging system during transportation

The process of assigning of each factor into different clusters of the MICMAC analysis diagram is performed by obtaining the driving power and dependence power from the Reachability matrix (Figure 12). For example, 'Product type' (2) got driving power of 11, and dependence power of 1. This means this factor can influence 11 other factors, and only one factor (i.e. itself) can influence it. Therefore, in the MICMAC Analysis diagram, the factor 'Product type' (2) will be placed in the point (11,1), where 11 corresponds to x axis and 1 to corresponds to y axis.

Even though a MICMAC Analysis diagram is usually self-explanatory, it is worth discussing the results. The below table (Table 10) shows the four cluster used:

Table 10 - Characteristics of each cluster in the MICMAC Analysis

Clusters	**Characteristics**
Independent variables	High driving power and low dependence
Linkage variables	Strong driving power and strong dependence
Autonomous variables	Weak driving and weak dependence
Dependent variables	Weak driving power but strong dependence

Independent variables

In the MICMAC Analysis, the most powerful factors are called 'Independent variables'. These factors have the strongest driving power, which means they can influence all the other factors, except the autonomous variables. Independent variables are not dependent to any other factors. Factors such as the 'size of the drug' (1), 'product type' (2), 'temperature range requirement of the drug' (3), 'temperature excursion tolerance level of the drug' (4), 'shipper's concern about the temperature profile of the country of origin and destination' (5) & 'time to market' (6) are Independent elements. They cannot be dependent on other factors. Among these decisive factors, 'Product Type' (2) has the strongest driving power than any other factors. This is clearly in alignment with the discussion with the drug manufacturer & the freight forwarder stated above.

The ‘temperature range of the drug’ (3) and the ‘temperature excursion tolerance level of the drug’ (4) being in close relation with the ‘product type’ (2) takes the second highest place and they also have very strong driving power on the cold chain packaging decision-making. Drug’s temperature requirement factors are specified by the drug manufacturer's laboratory. This will not change based on any actions taken by the manager. Even during our discussion with the drug manufacturer, they mentioned that ‘temperature range of the drug’ (3) and the ‘temperature excursion tolerance level of the drug’ (4) are the top factors taken into consideration as part of their internal decision-making process.

Another independent variable is the ‘size and weight of the drug shipment’ (1). We can see that ‘size and weight of the drug shipment’ (1), ‘temperature range of the drug’ (3) and ‘temperature excursion tolerance level of the drug’ (4) are all in the same influential level (Level 5) in the ISM diagram. However, the ISM does not show which factors, among these three, have the most driving power. But with the help of a MICMAC analysis, it is clear that ‘Temperature range of the drug’ (3) and ‘Temperature excursion tolerance level of the drug’ (4) have more driving power than ‘size and weight of the drug shipment’ (1) even though they belong to the same level in the ISM Diagram. This means that when a manager thinks of making a decision on what packaging system to be selected (active or passive), a little more importance has to be given to these two temperature related factors (‘temperature range of the drug’ (3) and ‘temperature excursion tolerance level of the drug’ (4)) than ‘size and weight of the drug shipment’ (1).

Another illustration of the benefit of MICMAC analysis can be understood by observing and comparing the placement of the factor ‘Time to market’ (6) in the ISM Diagram (14) and MICMAC Analysis Diagram (Figure 16). In the ISM Diagram, ‘Time to market’ (6) is placed at the Level 6 (which is the most influential level in the ISM diagram) that is equally at par with ‘Product type’ (2). But in the MICMAC Analysis diagram, the placement of ‘Time to market’ (6) got lesser driving power than other factors such as ‘temperature range of the drug’ (3) and

‘temperature excursion tolerance level of the drug’ (4). This is because ‘Time to market’ (6) is unable to influence decisive factors from (1) to (5). This is an example when a MICMAC analysis diagram is used as a supplement to the ISM Diagram because it is capable of showing the individual character of each factor. The ISM Diagram determines and shows the flow/levels of the decision-making process, but a MICMAC Analysis diagram shows each factor’s individual driving power and dependence power.

Linkage variables

A very interesting cluster in the MICMAC analysis is to understand the nature of the linkage variables. What makes them special is that they have both strong driving power and strong dependency on other factors. The factors such as ‘selection of distribution circuit’ and ‘actual distance to be travelled by the shipment’ are two linkage variables in our study. In the ISM Diagram, we can see four factors that lie at Level 3 which are ‘distance’ (7), distribution circuit (8), ‘shipper’s concern about the supervision and maintenance requirement’ (11) and ‘shipper’s concern about the reliable functioning of the packaging system’ (12). Here all these four factors are equally placed in the same level (Level 3). But what unites them are two linkage variables, which are distance (7) and distribution circuit (8). What makes them a linkage variable is their two-sided behavior. On one hand they are dependent on factors from (1) to (5), (11) & (12), and on the other hand, they are capable of driving other factors such as (9) to (12). That’s why they are considered as a linkage variable. So a manager should understand the special nature of these factors.

Dependent variables

Variables that have very low driving power, but are strongly dependent on other factors are called dependent variables. Factors like ‘cost of packaging’ (9), ‘shipper’s concern about the capacity of the packaging system to cope with unexpected temperature profile’ (10), ‘shipper’s concern about the supervision and maintenance of the packaging system during transportation’ (11) and ‘shipper’s

concern about the reliable functioning of the packaging system' (12) are dependent variables.

The best illustration would be to analyze the placement of 'cost of packaging' (9) in the MICMAC Analysis. The factor is placed at the very top left side of the diagram. It shows how this factor is dependent on all other factors.

Another example of a dependent variable is the 'shipper's concern about the capacity of the packaging system to cope with unexpected temperature profile' (10). A manager only has such concern when he/she is aware about the fact that this particular shipment contains temperature sensitive product (Factor 3 & 4) and is travelling long distances (Factor 7) through a distribution circuit (Factor 8) where the ambient temperature can be uncertain at times (Factor 5). It is the combination of all these facts that can make a manager concerned about this factor 'shipper's concern about the capacity of the packaging system to cope with unexpected temperature profile' (10). This shows how it is dependent on other factors.

Autonomous variables

Each factor is assigned into one of the four clusters as per the driving and dependence power derived from the Reachability Matrix (Figure 12). In our study, there is no autonomous variable.

Unexpected finding during our research

Based on the literature review, there were several decision factors that we expected to be part of this research. But during our interviews with the industry participants, we understood that some of these factors found in the literature were not used in real life by the shipper (drug manufacturer) and its freight forwarder. Therefore, the decisive factors listed below have been excluded from our study.

a) Cost of the drug – We expected the cost of the drug to influence the packaging decision, but both the drug manufacturer and the freight forwarder confirmed that it was not an important factor at all. The reason for this is that most of these

drug shipments were covered by insurance. Any damage borne will be reimbursed by the insurance companies. The freight forwarder mentioned that each party in the supply chain only has to pay $20/kilo in case of any loss or damage. So the actual cost of the drug is not an influencing factor at all. But this does not mean that shippers don't care about safe transportation. They will lose the customers or the business if the right product does not reach the final destination on time.

b) 'Shipper's concern about the risk hazard of the packaging system during transportation' was another factor that we included in our study initially. Some believed that since active systems are run by external power supply or lithium batteries, they were more hazardous (Romero, 2013). When we consulted the industry experts, they found this factor totally unnecessary, so we decided to remove it from our study.

c) 'Shipper's concern about using reusable close-loop passive packaging system due to environmental concern'.

- When this factor was discussed with the drug manufacturer, they replied that they cared more about the speed of delivery and the quality of the drug during transportation. They had very little interest in using a reusable closed loop system for their passive packaging containers. Even though they might be open to this idea in the future, as of now they are not keen about this initiative.
- When asked about reusable packaging container, the freight forwarder felt the main reason for the lack of interest was due to the complexity involved in it. They have tried a few times using reusable passive containers but they faced several problems such as damage to the packaging system caused by multiple use, lack of custom size for a particular shipment, lack of custom temperature setting for a particular product shipment, transportation cost of bringing the packaging container back to the country of origin and most importantly the complexity (transaction cost) involved in managing all these activities. Therefore, freight forwarders don't feel that this should be included in our study.

Potential factors

During our literature review, one of the most common keyword used when doing a research about cold chain was 'the regulation', especially the new GDP (Good Distribution Practices) regulation that differs from country to country. We expected this to be a strong decisive factor in the cold chain packaging decision-making but the freight forwarder didn't feel this was an important factor at the moment. They explained that storage areas of most airports (even in developed countries) are not fully equipped as per the requirements of the GDP regulation. The GDP regulation is not mandatory for international shipments where GDP rules may differ from country to country. GDP regulation only comes in importance during domestic transportation (i.e. the origin and destination is in the same country). But for domestic transportation, since the transportation time is normally between two to five hours, most shippers use refrigerator trucks for distribution. They try to use refrigerated trucks instead of using expensive packaging solutions. Therefore, regulation is not an important factor at the moment. But the participants feel that this may become more important in the coming years as more airports will have improved cold chain facilities.

Renaming the factors

During our interview with the drug manufacturer, they suggested us to rename the factor 'Temperature accuracy of the drugs' to 'Temperature excursion tolerance level'. So this has been updated in the final ISM Diagram in the Results section.

Measures for managing conflict of opinion within interviewed participants

Since we choose a semi-structured interview method, we were well aware about the possibility of conflict of opinion between the two participants (drug manufacturer and freight forwarder). To order to tackle this issue, we employed an industry expert (Freight Forwarder 2) who was a leader in the transportation of temperature-sensitive pharmaceutical products. The Freight Forwarder 2 had to act as an Independent Participant and had the following responsibilities

a) Verification of all individual assignments in the Final SSIM Matrix.

b) Verification of the placement of each factor at their respective levels (Level 6 through Level 1).
c) Explain the link (flow) between factors in one level to the factors in the subsequent level.
d) Suggestion for addition or elimination of any factors.
e) Usefulness of our results from the point of view of the industry expert.

The main purpose of the above mentioned verifications (a) & (b) were to provide assurance to the researcher that there was no conflicting opinion between the interviewed participants.

During the verification stage, there was a situation where the Independent Participant (Freight Forwarder 2) did not agree to some assignments made by the Interviewed Participants (Drug Manufacturer & Freight Forwarder 1). An example of a concern is the assignment made in 'SSIM for Drug Manufacurer' (Figure 7) and eventually removing the factor 'Cost of the drug' by the Interviewed Participants (Drug Manufacturer & Freight Forwarder 1). Freight Forwarder 2 felt that dollar value of the drugs was one of the primary factor that gave importance to the cold chain distribution, and hence had huge influence on the packaging system chosen. But as the facilitator of the interview provided explanations of the other interviewed participants, the Freight Forwarder 2 revised her opinion in light of the reply given by other interviewed participants and converged towards the 'original' answer or assignment. In the end, the Freight Forwarder 2 realized that the drug manufacturer's real concern about the dollar value was not actually the real cost of the product, but the loss of the potential to market those products and make huge profits within a specified time frame. The introduction of the new factor 'Time to Market' (6) by Freight Forwarder 1, and placement of this factor at the highest level (Level 6) in the ISM Diagram made Freight Forwarder 2 convinced about the removal of the factor 'Cost of the drug'. In the end, it was clearly evident that there was agreement between the Independent Participant (Freight Forwarder 2) and the Interviewed Participants (Drug Manufacturer & Freight Forwarder 1).

6. CONCLUSION

This thesis has stated the decisive factors involved in selecting a packaging system after consulting with various cold chain participants. An Interpretive Structural Modeling (ISM) methodology was used to conduct a detailed study of each of these factors. The resulting ISM Diagram has outlined the decision-making flow chart that explains the various stages (levels) in the decision-making process. The supplemental result, which is the MICMAC Analysis, provides more information about the individual characteristics of each factor (individual drive power and dependence) so the manager knows how much importance should be given to each of them.

An attempt has been made to qualitatively validate the results by an independent participant (an expert in the field of cold chain), who also explained about the practical usefulness of the results generated by this study. Based on the feedbacks from the independent industry expert, it was found that such a diagram showed a picture of the entire cold chain packaging decision-making process at one glance. Ignoring even a single factor from the diagram could have an adverse effect on the quality of the decision taken. Even though experienced managers are well aware of most of these factors intuitively, the ISM diagram will be useful for them to see a clearer picture of the various decision-making levels. When using this methodology, the participants can develop a deeper understanding of the meaning and significance of each decision element and the interrelations between these elements (Attri et al., 2013; Janes, 1988). Understanding the direct and indirect relationship between these decisive factors will show the situation far more accurately than an individual factor taken in isolation, giving the user a clear insight into the collective understanding of these relationships (Attri et al., 2013). It will assist decision makers in understanding what he/she really believes in and to recognize clearly what he/she does not know (Attri, Dev, & Sharma, 2013). All the results are communicated to the user in the combination of words and diagrams based on mathematics, where mathematics is hidden.

The independent participants also mentioned that such a research would be useful to educate new clients (drug manufacturer) about the various stages involved in the decision-making process. This will not only give more confidence to the client (drug manufacturer) about the freight forwarder' packaging decisions, but also an opportunity to involve the client's participation in the decision-making process.

In a competitive business world where pharmaceutical companies are facing fierce competition, they have to reduce cost and, at the same time, maintain highest quality of products and customer service. In such a context, our results should give them more confidence in their actions.

7. LIMITATIONS AND SCOPE FOR FUTURE RESEARCH

The results generated by this study are focused primarily on the cold chain packaging decision of bio-pharmaceutical drugs. Other cold chain products such as frozen food, fish, flower, semi-conductors etc. may have different factors to consider.

One should keep in mind that ISM is only a tool for determining the order (ranking) or flow of the decision-making process. It does not assign weightage to any elements (Govindan, Palaniappan, Zhu, & Kannan, 2012). Each company can assign different weightage of each factor. For example, different countries or even firms may have different sets of value and norms for environment.

Even though an attempt has been made to qualitatively validate the results by using an independent participant (an expert in the field of cold chain), there are other ways of validation too. Researchers such as (Pfohl, Gallus, & Thomas, 2011) have used two case study methods to test the practical applicability of the ISM results. In the first case study, the ISM result was evaluated through a well-guided process where the facilitator helped the participants to concentrate on the linkage between the elements. The second case study was less guided by the facilitator. The participant was asked to fill a questionnaire after a brief instruction. The results from the first case study method proved the usefulness of the ISM

methodology. Testing the validity of the results generated by a case study approach could be an area of future research.

However, this model has not been statistically validated yet. Literature suggest that models such as SEM (Structural Equation Modeling) which is also known as linear structural relationship approach have the capability of testing such hypothetical models. But there are differences between the ISM and SEM models. “A SEM model can statistically test an already developed ISM, but it cannot develop such an initial theoretical model. On the other hand, ISM has the capability to develop an initial theoretical model through managerial techniques such as brain storming, nominal group techniques etc.” (Govindan et al., 2010, p. 58). Therefore, ISM can be used as a supportive analytic tool for the decision making process under study (Govindan et al., 2010; Govindan et al., 2012; Ravi & Shankar, 2005).

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APPENDIX 1 : Questionnaire #1 - Drug Manufacturer

Dear (Drug Manufacturer),

Thank you for participating in my Master's Degree Thesis Project, which is based on Transportation of Temperature Sensitive Bio-Pharmaceuticals Products.

Purpose of the study

In cold chain the quality of services is heavily dependent on the investment in modern technology and equipment. Therefore we would like to study about the decisions made by managers in choosing those cold chain equipments, especially the cold chain packaging solutions.

Literature & Methodology

Based on various literature review, we found the following decisive factors the most important when it comes to selecting an ideal packaging solution.

1. Size & weight of the drug shipment
2. Cost of the drug
3. Actual distance to be travelled
4. Cost of Packaging (Selection between active vs. passive packaging system)
5. Temperature range requirement of the drug
6. Temperature accuracy requirement of the drug
7. Distribution circuit
8. Capacity of the packaging system to be flexible to the changing unexpected ambient temperature
9. Reliable functioning of the packaging system during transportation
10. Supervision and maintenance requirement during transportation
11. Concern of risk hazard during transportation
12. Use of reusable passive container due to concern for the environment

Note: A detailed explanation of each factor can be found at Appendix I. It will help us to understand how these factors are taken into consideration in the context of cold chain packaging solution.

Since the above-mentioned factors are both quantitative (distance, weight, size etc.) and qualitative (maintenance and supervision requirement, requirement of trained machine operators, hazard concern, impact on environment, product quality) in nature, it is difficult for managers to make uniform decisions when it comes to choosing a packaging solution. Even in the same business, different managers cultivated different mental models of the same situation. This plurality of mental modes among managers of the same industry leads to differences in opinion of the same given situation (Kassing, 2001). Normally these judgments are outcome of several factors such as the managers' history, memory, experience, anticipation, foresight, goal and values (Dagum, 1986). Researchers have used various 'think-tools' methodologies where qualitative factors can be expressed in mathematical terms in the form of binary relations (Bolanos, Fontela, Nenclares, & Pastor, 2005). Therefore

we decided to employ a powerful methodology called *Interpretive Structural Modeling (ISM).*

Anticipated benefits resulting from this study

The main goal of ISM is to assist decision makers to have a clear understanding of what he/she really believes in and to recognize clearly what he/she does not know (Attri, Dev, & Sharma, 2013). ISM methodology suggests the use of various techniques such as brain storming either from experts in industry or in academia to identify the contextual relationship among the factors (Debnath & Shankar, 2012; Govindan et al., 2012; Ravi & Shankar, 2005). This process will indirectly force the participant to state explicitly the interrelations between them (Janes, 1988). As a result, the participants can develop a deeper understanding of the meaning and significance of each element and the interrelations between these elements (Attri et al., 2013; Janes, 1988). By understanding the direct and indirect relationship between these decisive factors, we can see the situation far more accurately than an individual factor taken in isolation giving the user a clear insight into the collective understanding of these relationships (Attri et al., 2013). It will also show us the dependence and the drive power of each factor (Mandal & Deshmukh, 1994).

The beauty of the ISM is that it communicates the result to the user in the combination of words, diagram and mathematics, but where mathematics is hidden. ISM uses discrete mathematics logic and structure such as binary numbers, matrix theory, Boolean algebra etc. to demonstrate the relationship between elements (Janes, 1988).

Limitation of this methodology

One should keep in mind that ISM is only a tool for determining the order (ranking) or flow of the decision making process. It does not assign weightage to any elements (Govindan, Palaniappan, Zhu, & Kannan, 2012). Each company can assign different weightage of each factor. For example, different countries or even firms may have different sets of value and norms for environment standards.

Description of how confidentiality will be assured

This study has been reviewed and approved by HEC Montreal's Ethics Committee (CER). CER has determined that this study meets the ethical obligations required by the University's policies. Therefore you will be assured of complete confidentiality.

QUESTIONNAIRE

Since we have already gathered the various decisive factors (elements), a Structural Self-Interaction Matrix (SSIM) is developed based on the pairwise comparison of these elements. SSIM is a brain storming technique to identifying the contextual relationship among the factors (Debnath & Shankar, 2012; Govindan et al., 2012; Ravi & Shankar, 2005). These processes will indirectly forces the participants to state explicitly the interrelations between them (Janes, 1988).

For understanding the contextual relationship, we will ask ourselves four questions and denote a symbol. In order to analyze the relationship among the elements, a contextual relationship will be developed by four symbols (V, A, X and O). These symbols denote the relationship between factor i and j:

- V: if decisive factors 'i' will influences decisive factors 'j';
- A: if decisive factors 'j' will influences decisive factors 'i';
- X: if decisive factors 'i' and 'j' will influence each other; and
- O : if decisive factors 'i' and 'j' does not influence each other.

STRUCTURAL SELF-INTERACTION MATRIX (SSIM)

	i	12	11	10	9	8	7	6	5	4	3	2	1
j	Decisive factors in choosing packaging system	Impact on environment	Risk of hazard during transportation	Maintenance and supervision requirement during transportation	Reliability of the packaging system	Flexibility of the packaging system to change to unexpected ambient temperature	The distribution circuit	Temperature accuracy requirement of the drug	Temperature range of the drug	Cost of packaging	Distance to be travelled	Cost of the drug	Size and volume of the product
1	Size and volume of the product	O	O							V		O	
2	Cost of the drug	O	O	O	O	O	O	O	O	O	O		
3	Distance to be travelled	O	O							V			
4	Packaging cost	O	O				A	A	A				
5	Temperature range of the drug	O	O										
6	Temperature accuracy requirement of the drug	O	O										
7	The distribution circuit	O	O		X								
8	Flexibility of the packaging system to change to unexpected ambient temperature	O	O										
9	Reliability of the packaging system	O	O										
10	Maintenance and supervision requirement during transportation	O	O										
11	Risk of hazard during transportation	O											
12	Impact on environment												

Since we value and respect your time, we will limit our questions only to few decisive factors (elements). We intend to ask your opinion on interrelations of only few elements only that are grey shaded area on the matrix above.

Question 1 **- Will the 'cost of the drug' (2) influence the shipper to change the 'distribution circuit' (7)?**

From your experience, have you requested your logistics providers to use a special transportation route (use of direct flight instead of flight connecting through several hubs) primarily because the drug was very expensive?

This will help us understand if the cost of the drug (2) can influence the decision of selection of distribution circuit (7).

The 'cost of the drug' will not affect the distribution circuit used. It is only the drug manufacturer who knows the actual content and cost of the each drug shipment. This information is not shared with any other players in the cold chain, not even the freight forwarder. 'Cost of the drug' (2) will have no influence on any factors in the cold chain packaging decision-making. So 'O' should be denoted to all other factors in the SSIM connected with 'cost of the drug' (2).

Question 2 **- Will the 'cost of packaging' (4) influence the shipper to change the 'distribution circuit' (7) used?**

Here we assume that an active packaging system is expensive compared to the passive packaging system. Based on your experience, have you ever changed your distribution circuit (direct flight vs. connecting flight vs. intermodal transportation etc.) because you are using a particular packaging system (active or passive packaging system)?

This will help us understand if the 'cost of packaging' (4) can influence the 'shipper's decision in distribution route selection' (7).

The 'cost of packaging' will not change the 'distribution circuit' used. But 'cost of packaging' will change depending on the 'distribution circuit' used, especially in the case of International shipments (which means distance). So 'distribution circuit' (7) and the 'distance' (3) can influence the 'cost of packaging' (4). Therefore 'A' will be denoted in the above SSIM matrix in the cell 4-7, and 'V' in SSIM matrix 3-4.

Question 3 **- Will selection of a particular 'distribution circuit' (7) influence the 'shipper's concern about the reliable functioning of the packaging system during transportation' (9)?**

Since active packaging systems are run by mechanical force and external power supply, there always exist a chance of mechanical failure. On the other hand, since passive packaging system is not controlled by any mechanical force, they are less chance of mechanical failure or breakdown. Therefore they are considered to be more reliable system in terms of their functioning (Romero, 2013).

Have you ever experienced a situation where selection of a particular distribution circuit (route or path) has caused an additional risk to proper functioning of packaging system? This information will help us to understand if the distribution circuit selected by the shipper (7) can influence the reliability of the selected packaging system (9).

When a temperature sensitive drug is transported by an active packaging system, it must be distributed through a preplanned route and network where adequate facilities are available. So the distribution circuit is always planned accordingly. This is done in order to maintain the reliable functioning of the selected packaging system. So both are very dependent to each other, therefore 'X' will be denoted to above SSIM Matrix in the cell 7-9.

Question 4 **- Is there any decisive factors (elements) we are missing?**

Yes, there is one important facto that is missing in study, which is **'Product Type'.** Product types are classified under different names such as 'Vaccines', 'Bio-similar', 'Oncology',' Narcotics' etc. Irrespective of the 'temperature range requirement' or 'temperature extrusion tolerance level', these product types are the main criteria for forming SOP (Standard Operating Procedures). So they should be included in your study too.

Question 5 **- Based on the decisive factors we have collected from literature, could you explain which elements do your company gives more or less importance?**

a) Concern about Environment – Drug manufacturers is more concerned with patient's health safety than environmental impact, so these drugs are transported in the quickest and safest way. We would like to take consideration of environment but if it affects the speed of our delivery or risk the quality of the drug, then environment concern will be ignored. So I think it is not an important factor in a cold chain packaging decision-making.

b) Risk Hazard – Hazard risk of containers during distribution is not a concern at all. It is obvious that there is no hazardous risk in passive packaging system. But even while transporting in active packaging system, we use batteries or dry ice that never caused any hazard so far. So I think that factor should be removed from your study.

c) Temperature accuracy requirement of the drug – This name should be renamed to 'Temperature excursion tolerance level' as this is more commonly used term in our industry.

d) '*Product Type'* should be included in your study**. →Mentioned above *(Very important)***

Question 6 – Can you explain the relationship of the factor you suggested, which is 'Product type' with other factors in our SSIM Matrix.

STRUCTURAL SELF-INTERACTION MATRIX (SSIM)
For Drug Manufacturer

	i	13	12	11	10	9	8	7	6	5	4	3	2	1
j	Decisive factors in choosing packaging system	Impact on environment	Risk of hazard during transportation	Maintenance and supervision requirement during transportation	Reliability of the packaging system	Flexibility of the packaging system to change to unexpected ambient temperature	The distribution circuit	Temperature accuracy requirement of the drug	Temperature range of the drug	Cost of packaging	Distance	Cost of the drug	Size and volume of the product	Product type
1	Product type	O	O	V	V	V	V	V	V	V	V	O	V	-

In order to analyze the relationship among the elements, a contextual relationship will be developed by four symbols (V, A, X and O). These symbols denote the relationship between factor i and j:
- V: if decisive factors 'i' will influences decisive factors 'j';
- A: if decisive factors 'j' will influences decisive factors 'i';
- X: if decisive factors 'i' and 'j' will influence each other; and
- O : if decisive factors 'i' and 'j' does not influence each other.

It is important to note that some elements cannot be connected with each other because they are no of the same nature. In such cases, symbol 'O' will be denoted.

***Question 7* – Is there any decision making process your company uses when it comes to selection of a packaging system?**

We do have our own way in deciding on our packaging system. It's also helpful for our quality assurance. We follow two stages.

In the 1st stage, a packaging system will be selected based on major decisive factors use as 'cost of the packaging', 'space consumed by the shipment', 'temperature range requirement', 'temperature excursion tolerance level' and the 'distance' to be transported

In the 2nd stage, the detailed quality assurance testing is done where the freight forwarder will provide a mock packaging solution according to the specification given by us (drug manufacturer). This packaging system will be tested for quality assurance.

Thank you for your assistance!

APPENDIX 2: Questionnaire #2 - Drug Manufacturer

ADDITIONAL QUESTION

1. What kind of cold chain packaging system do you normally use during normal and extreme weather conditions? Is it Active or Passive system?

> We use both packaging system throughout the year. But for passive packaging system, we use special additional cooling components to cope the extreme weather.

2. For Passive Packaging system, what types of components do you use? How do you determine the ideal amount of cooling components? Is there any particular method used by your company?

> We do have our own way in deciding on our packaging system that also includes a quality assurance program too. We follow two stages approach:
>
> In the 1st stage, a packaging system will be selected based on major decisive factors For example, 'cost of the packaging', 'space consumption of the shipment', and 'actual distance to be travelled'.
>
> In the 2nd stage, the detailed quality assurance test is done where the freight forwarder will design a mock packaging solution according to the specification given by us (drug manufacturer) based on the product type. This mock packaging system will be tested for quality assurance. Only after the testing process, we will implement that packaging solution for real use. The freight forwarder may use multiple cooling component ranging from gel pack, thermal blanket etc. This is the job of the freight forwarder to find the right mix of the cooling components.

3. Have you ever used an active packaging system? If yes, how was your experience? Did you encounter any problems (hazardous risk)? What are the solely reasons which makes you think of passive packaging system as an alternative?

> We (our company and our sister concern in USA) still use active packaging very often. Mainly because it is very reliable when it comes to maintaining the required temperature.. We never faced any hazardous concern related to the packaging system. But we mainly use passive packaging solution when the 'size and weight of the shipment' is small. When it isn't affordability to use active packaging container for those small items. So 'cost of packaging' is an important factor.

4. Who has the most power in selecting a packaging system? Is it the drug manufacturer or the freight forwarder? If it is the freight forward, then isn't it the drug manufacturer who is facing the negative image.

> We have the full control on deciding which packaging solution should be used. It is our duty to keep ourselves updated about the latest cold chain packaging solution. Then we ask our freight forwarder to provide us those services. We are always open in taking suggestion from the freight forwarders.

5. Are you satisfied with the decisions taken by the freight forwarder?

> No one is perfect, but we are satisfied their service.

6. Do you face situations where your product has to cross through multiple weather condition? E.g. Canada —> Africa ——> Russia. Since this distribution circuit is complicated, what packaging solution and components do you use?

If depends. If its domestic distribution, we use passive packaging system with better components.

For international shipment, we will use passive or active depending on the distribution network.

7. Do any of you customers request for a special type of packaging system? If yes, do you normally try to satisfy that request? Do you do the same kind of request to your suppliers too?

Our customers do not demand for a certain packaging solution. But we demand our suppliers for certain packaging solutions. This is because we are liable to accept the return of the product to our customer. While we don't have that advantage with our suppliers.

8. Its about the concern for environment - Is your packaging system under a closed loop where they come back to you or is it scraped by the final user?

As a drug manufacture, our most important concern is patient safety, so we transport the drugs in the quickest and safest way. We don't mind being concern about the environment. But if they affect the speed of delivery and quality of the drug; then the environment concern will be ignored. But we are open to learning about way can be more environment friendly.

9. Do you have any future plans or initiative in improving your cold chain functioning, especially in the area of packaging?

Currently, we are learning of new packaging solution using Phase Change Materials (PCM). Earlier, this use to be very expensive. We have found cheaper PCM in market these days. We are working on testing them. This can be used in our passive packaging solutions.

10. Do you take any precaution against freezing of these temperature sensitive products, especially during the winter?

Yes. As mentioned earlier, we have special packaging solutions for extreme winter to tackle the problem of freezing. The freight forwarder takes care of this issues as it is very technical.

GENERAL QUESTION

11. What kind of temperature monitoring device do you use a) PDF Data Logger b) RFID Data Logger c) Chemical Data Logger

We use USB Data Logger. The data will be stored in the USB that will be uploaded upon arrival to final destination. This information is stored to our centralized database server that can be accessed from anywhere. We can see the temperature excursion, if any and take necessary actions.

APENDIX 3 : Questionnaire - Freight Forwarder 1

Dear (Freight Forwarder)

Thank you for participating in my Master's Degree Thesis Project, which is based on Transportation of Temperature Sensitive Bio-Pharmaceuticals Products.

Purpose of the study

In cold chain the quality of services is heavily dependent on the investment in modern technology and equipments. Therefore we would like to study about the decisions made by managers in choosing those cold chain equipments, especially the cold chain packaging solutions.

Research question

c) What are the most important decisive factors in selecting a cold chain packaging system?
d) What is the inter-relation between these factors?
e) How these elements helps in the decision making process.

Literature & Methodology

Based on various literature review and interview with the drug manufacurer, we found the following decisive factors the most important when it comes to selecting an ideal packaging solution.

13. Size & volume of the product
14. Cost of the drug
15. Distance
16. Packaging cost (Active Vs. Passive)
17. Temperature range of the drug
18. Temperature accuracy requirement of the drug
19. Distribution circuit
20. Flexibility/requirement of the packaging system to the change to unexpected ambient temperature
21. Reliability of the packaging system
22. Maintenance and supervision requirement during transportation
23. Impact on the environment
24. Product type

Note: A detailed explanation of each factor can be found at Appendix I. It will help us to understand how these factors are taken into consideration in the context of cold chain packaging solution.

Since the above-mentioned factors are both quantitative (distance, weight, volume) and qualitative (maintenance and supervision requirement, requirement of trained machine operators, hazard concern, impact on environment, assuring product quality) in nature, it is difficult for managers to make uniform decisions when it comes to choosing a packaging solution. Even in the same business, different

managers cultivated different mental models of the same situation. This plurality of mental modes among managers of the same industry leads to differences in opinion of the same given situation (Kassing, 2001). Normally these judgments are outcome of several factors such as the managers' history, memory, experience, anticipation, foresight, goal and values (Dagum, 1986). Researchers have used various 'think-tools' methodologies where qualitative factors can be expressed in mathematical terms in the form of binary relations (Bolanos, Fontela, Nenclares, & Pastor, 2005). Therefore we decided to employ a powerful methodology called *Interpretive Structural Modeling (ISM).*

Anticipated benefits resulting from this study

The main goal of ISM is to assist decision makers to have a clear understanding of what he/she really believes in and to recognize clearly what he/she does not know (Attri, Dev, & Sharma, 2013). ISM methodology suggests the use of various techniques such as brain storming either from experts in industry or in academia to identify the contextual relationship among the factors (Debnath & Shankar, 2012; Govindan et al., 2012; Ravi & Shankar, 2005). This process will indirectly force the participant to state explicitly the interrelations between them (Janes, 1988). As a result, the participants can develop a deeper understanding of the meaning and significance of each element and the interrelations between these elements (Attri et al., 2013; Janes, 1988). By understanding the direct and indirect relationship between these decisive factors, we can see the situation far more accurately than an individual factor taken in isolation giving the user a clear insight into the collective understanding of these relationships (Attri et al., 2013). It will also show us the dependence and the drive power of each factor (Mandal & Deshmukh, 1994).

The beauty of the ISM is that it communicates the result to the user in the combination of words, diagram and mathematics, but where mathematics is hidden. ISM uses discrete mathematics logic and structure such as binary numbers, matrix theory, Boolean algebra etc. to demonstrate the relationship between elements (Janes, 1988).

Limitation of this methodology

One should keep in mind that ISM is only a tool for determining the order (ranking) or flow of the decision making process. It does not assign weightage to any elements (Govindan, Palaniappan, Zhu, & Kannan, 2012). Each company can assign different weightage of each factor. For example, different countries or even firms may have different sets of value and norms for environment.

Description of how confidentiality will be assured

This study has been reviewed and approved by HEC Montreal's Ethics Committee (CER). CER has determined that this study meets the ethical obligations required by the University's policies. Therefore you will be assured of complete confidentiality.

QUESTIONNAIRE

Since we have already gathered the various decisive factors (elements), a Structural Self-Interaction Matrix (SSIM) is developed based on the pairwise comparison of these elements. SSIM is a brain storming technique to identifying the contextual relationship among the factors (Debnath & Shankar, 2012; Govindan et al., 2012; Ravi & Shankar, 2005). These processes will indirectly forces the participants to state explicitly the interrelations between them (Janes, 1988).

For understanding the contextual relationship, we will ask ourselves four questions and denote a symbol. In order to analyze the relationship among the elements, a contextual relationship will be developed by four symbols (V, A, X and O). These symbols denote the relationship between factor i and j:

- V: if decisive factors 'i' will influences decisive factors 'j';
- A: if decisive factors 'j' will influences decisive factors 'i';
- X: if decisive factors 'i' and 'j' will influence each other; and
- O : if decisive factors 'i' and 'j' does not influence each other.

STRUCTURAL SELF-INTERACTION MATRIX (SSIM)
Questionnaire for Freight Forwarder

	i	10	9	8	7	6	5	4	3	2	1
j	Decisive factors in choosing packaging system	Shipper's concern about the reliable functioning of the packaging system during transportation	Shipper's concern about the supervision and maintenance requirement during transportation	Shipper's concern about the capacity of the packaging system to be flexible to unexpected ambient temperature	Packaging cost	Selection of distribution circuit	Distance to be travelled	Temperature excursion tolerance level	Temperature range requirement of the drug	Product type	Size and weight of the drug shipment
1	Size and weight of the drug shipment	V	V	O	V	V	V	O	O	A	-
2	Product type	V	V	V	V	V	V	V	V		
3	Temperature range requirement of the drug	V	V	V	V	V	V	O			
4	Temperature excursion tolerance level	V	V	V	V	V	V				
5	Distance to be travelled	X	X	V	V	X					
6	Selection of distribution circuit	X	X	V	V						
7	Packaging cost	A	A	A							
8	Shipper's concern about the capacity of the packaging system to be flexible to unexpected ambient temperature	O	O								
9	Shipper's concern about the supervision and maintenance requirement during transportation	X									
10	Shipper's concern about the reliable functioning of the packaging system during transportation										

Since we value and respect your time, we will limit our questions only to few decisive factors (elements). We intend to ask your opinion on interrelations of only few elements only that are grey shaded area on the matrix above.

a) Will the 'size and weight of the drug shipment '(1) influence the type of packaging system (7) selected by the shipper?

Yes, The 'size and weight of the drug shipment' has a strong influence on the type of packaging system used.

If the 'size and weight of the drug shipment' is small then we cannot justify the cost of using an expensive active container (which has large in space capacity), therefore a passive container (which is normally smaller in size and can be custom made) will be considered because it is very cheap compared to active packaging systems.

But if the 'size and weight of the drug shipment' is large, then we may consider using an active packaging system because we can justify the extra cost of using an active container. So we don't mind taking extra space by using an active container.

b) Will the type of packaging system (7) selected by the shipper influence the 'size and weight of the drug shipment' (1)?

No.

c) Will the 'size and weight of the drug shipment' (1) influence a change in the 'distribution network' (6)?

Yes, the 'size and weight of the drug shipment' can influence on decision on which distribution circuit to use. We have experienced several situations where the drug shipments (containers) were large in size and we were unable to load the container into a particular aircraft. Airplanes that were designated specially for cargo have much larger capacity, but when we rely on the passenger planes we only have limited space beneath the passenger floor. So at times, when our shipments were large in size, we used alternative aircraft and routes for distribution. Small containers are easy to fit into the most airplanes.

d) Can the 'size and weight of the drug shipment' (1) influence the 'shipper's concern about the capacity of the packaging system to be flexible to unexpected ambient temperature' (8)?

No, size of the shipment has no relationship with this concern

e) Can the 'distribution circuit' (6) selected increase or decrease the 'size and weight of the drug shipment' (1)?

No.

f) Will the 'size and weight of the drug shipment' (1) increase or decrease the 'distance travelled by the drug shipment' (5)?

As discussed earlier, the 'size and weight of the drug shipment' can change the airplane used and also the 'distribution circuit used'. If the distribution routes change, it can increase or decrease the 'actual distance travelled' by the shipment.

g) Can the 'distance travelled by the shipment' (5) increase or decrease the 'size and weight of the drug shipment' (1)?

No.

h) Will the 'size and weight of the drug shipment' (1) change the 'temperature excursion tolerance level' (4)?

No.

i) Can the 'temperature excursion tolerance level' (4) change the 'size and weight of the drug shipment' (1)?

No.

j) Can the 'size and weight of the drug shipment' (1) change the 'temperature range of the drug' (3)?

No.

k) Can the 'temperature range of the drug' (3) can the 'size and weight of the drug shipment' (1)?

No.

l) Can the 'temperature range of the drug' (3) and 'temperature accuracy requirement of the drug' (4) influence you to choose a particular 'distribution circuit' (6)?

Yes, the 'temperature range of the drug' and 'temperature accuracy requirement of the drug' can influence our decision to choose a particular 'distribution circuit'. Some drug products are very delicate and have to be distributed through hubs that got good infrastructure and staff to supervise the containers.

m) Can a particular 'distribution circuit' (6) can the 'temperature range requirement of the drug' (3) and the 'temperature accuracy requirement of the drug' (4)?

No.

n) Can the 'temperature range of the drug' (3) and 'temperature accuracy requirement of the drug' (4) can increase or decrease the actual 'distance travelled' (5)?

Yes, as mentioned before the 'temperature range of the drug' and 'temperature accuracy requirement of the drug' can influence our decision to choose a particular 'distribution circuit'. Some drug products are very delicate and have to be distributed through hubs that got good infrastructure and staff to supervise the containers. The actual distance travelled by the drug shipment can change depending on the distribution circuit used.

o) Can the 'temperature range requirement of the drug' (3) and 'temperature excursion tolerance level' (4) can influence the 'shipper's concern about the

capacity of the packaging system to be flexible to unexpected ambient temperature' (8)?

Yes, I think these temperatures requirement of the drug can influence the 'shipper's concern about the capacity of the packaging system to be flexible to unexpected ambient temperature'.

p) Can the 'temperature range requirement of the drug' (3) and 'temperature excursion tolerance level' (4) influence the 'shipper's concern about the supervision and maintenance required during transportation' (9)?

In cold chain, every temperature sensitive product requires constant supervision. So yes, these temperature requirement factors can influence the 'shipper's concern about the supervision and maintenance required during transportation'.

q) Can the 'temperature range requirement of the drug' (3) and 'temperature excursion tolerance level' (4) influence the 'shipper's concern about the reliable functioning of the packaging system during transportation' (10)?

Yes, if the product got narrow temperature ranges requirement and small temperature excursion tolerance level, then a more reliable packaging system will be preferred.

r) Can a particular 'distribution circuit' (6) or 'distance travelled' (5) change the 'temperature range requirement of the drug' (3) and the 'temperature accuracy requirement of the drug' (4)?

No.

s) What is the relationship between 'distribution circuit' (6) and 'distance travelled by the shipment' (5)?

Both are interrelated and can influence each other

t) Can the 'Cost of packaging' (7) influence the 'shipper's concern about the capacity of the packaging system to be flexible to unexpected ambient temperature' (8)?

No, it's the opposite. The packaging decision is made after considering about the need for such features.

u) Can the 'shipper's concern about the capacity of the packaging system to be flexible to unexpected ambient temperature' (8) make him/her choose a different packaging system (7)?

Yes. If the shipper is concern about this, they might use an active packaging system.

v) Can the choice between an active and passive packaging system (7) influence the 'shipper's concern about the supervision and maintenance requirement during transportation' (9)?

No. This concern is taken care off before selecting the packaging system.

w) Can the 'shipper's concern about the supervision and maintenance required during transportation' influence the decision to choose a particular packaging system (7)?

Yes. Only if the shipper has enough capacity to make constant supervision and maintenance, then he/she will opt for an active packaging system. Otherwise, a passive packaging system is considered.

x) Can the choice between an active and passive packaging system (7) influence the 'shipper's concern about the reliable functioning of the packaging system' (10)?

No. This concern is taken care off before selecting the packaging system.

y) Can the 'shipper's concern about the reliable functioning of the packaging system' (10) influence the decision to choose a particular packaging system (7)?

Yes. If the shipper is concern about the reliable of the packaging system, an appropriate packaging system will be chosen.

z) Is there is any relationship between the 'shipper's concern about the flexibility of the packaging system to unexpected ambient temperature' (8) and 'shipper's concern about the reliability of the packaging system' (10)?

No, there is no relation between them.

aa) What is the relationship between the 'shipper's concern about the flexibility of the packaging system to unexpected ambient temperature' (8) and the 'shipper's concern about the maintenance and supervision requirement during transportation' (9)?

No, there is no relation between them. No human intervention is required for the active containers to cope with unexpected ambient temperature.

bb) What is the relationship between 'shipper's concern about the supervision and maintenance requirement during transportation' (9) and the 'shipper's concern about the reliable functioning of the packaging system' (10)?

Both the factors are interconnected. 'Shipper's concern about the supervision and maintenance' can influence the 'concern about the reliable functioning of the packaging system'. Shipper's concern about the safe functioning is dependent on what kind of supervision is available during transportation and at each connecting hubs. There have been situations where the some connecting hubs (airport) did not have the adequate power socket to charge the active packaging containers. In such cases, the operator has to find an immediate remedial action.

cc) Can the 'shipper's concern about the capacity of the packaging system to be flexible to unexpected ambient temperature' (8) change the 'distribution circuit' (6) the 'actual distance travelled' (5)?

No. It's the opposite. Then distance between two countries and the distribution circuit selected can increase or decrease the 'shipper's concern about the capacity of the packaging system to be flexible to unexpected ambient temperature'.

dd) Can 'shipper's concern about the supervision and maintenance required during transportation' (9) influence the 'distribution circuit' used by the shipper (6) and the 'actual distance travelled' (5)?

Yes. Very similar to the situation above. Operators are required at each hub for supervision and maintenance, if required. This can influence the shipper to choose a particular distribution circuit that may have these operators and required infrastructure for maintenance (socket for charging the active container).

ee) Can the 'distribution circuit used by the shipper' (6) and the 'actual distance travelled' (5) influence the 'shipper's concern about the supervision and maintenance required during transportation' (9)?

Yes, The distribution circuit selected should have trained staffs to perform supervision and maintenance. So these they can influence the shipper's concern.

ff) Can 'shipper's concern about the reliable functioning of the packaging system' influence the 'distribution circuit' used by the shipper (8) and the 'actual distance travelled' (5)?

Yes. Some distribution circuits are safer for transporting certain packaging containers. In some airports the waiting time on tarmac area is longer than other airports. If the connecting hubs are in countries where they experience extreme temperature (e.g. -40 degree Celsius), then an active container may stop functioning. So shipper prefer to use distribution circuit will be facilitate safe functioning of the packaging system.

gg) Is there any other decisive factor (element) we could be missing? If yes, we would like to discuss in-person the interrelation of that element with other elements.

Yes, I would recommend you two factors
1) Time to market &
2) Shipper's concern about the temperature profile of the country of origin and destination.

'Time to market' is a very important factor because it can influence most of the other factors. There are situation where our client (i.e. the drug manufacturer) wanted to bring a drug product to the market on a specific date and there was lack of time to design, validate and send the passive container to the seller in Asia. In spite of our recommendation to use a passive packaging system, our client prefer to use an active packaging system which cost them an extra $30,000 for that shipment. We (drug manufacturer and the freight forwarder) made sure we transported it the safest distribution route. We also performed constant supervision throughout the shipment's entire journey. So 'time to market' is a very important factor.

Concern about the temperature of the origin and destination country is also a factor we take consideration before making a packaging decision. We study about

the expected temperature of these countries and then make packaging decisions accordingly.

hh) Can you explain the relationship between the factors 'Time to market' and 'Shipper's concern about the temperature of the origin and destination country' with all other factors in our SSIM Matrix?

STRUCTURAL SELF-INTERACTION MATRIX (SSIM)

Decisive factors in choosing packaging system	Reliability of the packaging system	Maintenance and supervision requirement during transportation	Flexibility of the packaging system to changing ambient temperature	Packaging cost	The distribution circuit	Distance to be travelled	Temperature accuracy requirement of the drug	Temperature range requirement of the drug	Product type	Size and weight of the drug	Time to market	Concern about the temperature profile of the origin and destination country
Concern about the temperature profile of the origin and destination country	V	V	V	V	V	V	A	A	A	O	O	-
Time to market	V	V	V	V	V	V	O	O	O	O	-	

V: if decisive factors 'i' will influences decisive factors 'j';
A: if decisive factors 'j' will influences decisive factors 'i';
X: if decisive factors 'i' and 'j' will influence each other; and
O : if decisive factors 'i' and 'j' does not influence each other.

ii) During our interview with the drug manufacturer, they recommended us to remove three factors, which was as follows:
a) Cost of the drug
b) Shipper's concern about using reusable passive packaging containers due to environmental concern
c) Shipper's concern about the risk hazard during transportation.

Since we were convinced, we have removed them from our study. What is your opinion?

Yes. The drug manufacturer's recommendation to remove those factors makes perfect sense due to the following reasons:

a) Cost of the drug – Freight forwarder is unaware about the actual cost of the drug. We do our job depending on what is mentioned in the SOP (Standard Operating Procedure). And most of these bio-pharmaceutical products are insured; therefore pharma companies will be reimbursed if any damage takes place. From the freight forwarder point of view, we are only liable for an amount of $20/kilo. So this is a very small liability from our side, rest is taken care by the insurance companies. So I don't think so that 'cost of the drug' is an important factor in selecting a packaging solution. But we both the drug manufacturer and us try our best to make the product available to the final consumer at the best quality.
b) Shipper's concern about the risk hazard during transportation – We have not faced any hazardous situation earlier. Therefore I also agree with the drug manufacturer's statement.

c) Shipper's concern about using reusable passive packaging containers due to environmental concern – Earlier we have tried taking imitative in using reusable passive packaging system taking in account of the environment concern. But we had stopped it because of the complexity involved in managing it. The main difficulty were a) the damage caused to these passive containers which had to be repaired and replaced before reuse b) the complexity involved in bring these empty containers back to the shipper's country of origin c) The transportation cost connected with bringing these empty container back. Such scenarios took a lot of valuable time of the management. Therefore we have stopped using them for the time being until we find a easier way to deal it.

jj) During our literature review, we have found that much literature relating to cold chain gave huge importance to the GDP (Goods Distribution Practice) regulation. Do you think it should be one of the decisive factors to be included in our study?

GDP Regulation is the most important topic in the cold chain today. But I don't think it's time for us to include it in your study. This is because most of the international airport does not have the infrastructure or facilities to follow the current GDP regulations. Also, it is not practical to follow them. For example, one of the GDP principles is that vaccines must be transported with fish or meat products. But this may not possible in real life.

Therefore most of the drug shipments hardly follow these regulations.

Since GDP regulation varies from country to country, there is also no uniformity. So when we do an international transportation, we don't follow GDP.

However, GDP regulations are followed when drugs a are distributed domestically (within the same country) because it falls under one country's GDP rules. But most of the time, when the shipments are transported within the same country, shippers don't invest in expensive packaging system. They tried to compensate it the packaging cost by using refrigerated trucks with controlled-temperature.

Therefore, I don't think you should include it in your study at the moment because it is not widely used by most of us. It may take some years for all the airports to have the necessary infrastructures to follow the GDP rules.

Thank you for your assistance

APPENDIX 4 : Questionnaire – Freight Forwarder 2 (For validation purpose)

Dear (Freight Forwarder),

Thank you for participating in my Master's Degree Thesis Project, which is based on Cold Chain.

Purpose of the study

In cold chain the quality of services is heavily dependent on the investment in modern technology and equipments. Therefore we would like to study about the decisions made by managers in choosing those cold chain equipments, especially the cold chain packaging solutions.

Research question

f) What are the most important decisive factors in selecting a cold chain packaging system?
g) What is the inter-relation between these factors?
h) How these elements helps in the decision making process.

Literature & Methodology

Based on various literature review and interview with the drug manufacturer, we found the following decisive factors the most important when it comes to selecting an ideal packaging solution.

25. Size & volume of the product
26. Cost of the drug
27. Distance between the country of origin and destination
28. Distribution circuit to be used
29. Packaging cost (Selection between active vs. passive packaging system)
30. Product type (vaccines vs. insulin vs. blood components vs. narcotics)
31. Temperature range requirement of the drug
32. Temperature excursion tolerance level of the drug
33. Shipper's concern about the temperature profile of the country of origin and destination.
34. Shipper's concern about the flexibility of the packaging system to change in times of unexpected ambient temperature.
35. Shipper's concern about the reliable functioning of the packaging system during transportation.
36. Shippers' concern about the supervision and maintenance requirement during transportation
37. Shipper's concern about impact on the environment (Use of reusable passive packaging container in a closed-loop distribution circuit)
38. Time to market (Drug manufacturer's urgency to bring the product to the market on time)

Since the above-mentioned factors are both quantitative (distance, weight, volume) and qualitative (maintenance and supervision requirement, requirement of trained machine operators, hazard concern, impact on environment, assuring product quality) in nature, it is difficult for managers to make uniform decisions when it comes to choosing a packaging solution. Even in the same business, different managers cultivated different mental models of the same situation. This plurality of mental modes among managers of the same industry leads to differences in opinion of the same given situation (Kassing, 2001). Normally these judgments are outcome of several factors such as the managers' history, memory, experience, anticipation, foresight, goal and values (Dagum, 1986). Researchers have used various 'think-tools' methodologies where qualitative factors can be expressed in mathematical terms in the form of binary relations (Bolanos, Fontela, Nenclares, & Pastor, 2005). Therefore we decided to employ a powerful methodology called *Interpretive Structural Modeling (ISM).*

Anticipated benefits resulting from this study

The main goal of ISM is to assist decision makers to have a clear understanding of what he/she really believes in and to recognize clearly what he/she does not know (Attri, Dev, & Sharma, 2013). ISM methodology suggests the use of various techniques such as brain storming either from experts in industry or in academia to identify the contextual relationship among the factors (Debnath & Shankar, 2012; Govindan et al., 2012; Ravi & Shankar, 2005). This process will indirectly force the participant to state explicitly the interrelations between them (Janes, 1988). As a result, the participants can develop a deeper understanding of the meaning and significance of each element and the interrelations between these elements (Attri et al., 2013; Janes, 1988). By understanding the direct and indirect relationship between these decisive factors, we can see the situation far more accurately than an individual factor taken in isolation giving the user a clear insight into the collective understanding of these relationships (Attri et al., 2013). It will also show us the dependence and the drive power of each factor (Mandal & Deshmukh, 1994).

The beauty of the ISM is that it communicates the result to the user in the combination of words, diagram and mathematics, but where mathematics is hidden. ISM uses discrete mathematics logic and structure such as binary numbers, matrix theory, Boolean algebra etc. to demonstrate the relationship between elements (Janes, 1988).

Present situation

Some the factors mentioned above have being eliminated as suggested by the participants that include drug manufacturer and freight forwarder specializing in distribution of temperature-sensitive shipment (cold chain). Based on several techniques such as brainstorming, Q & A session etc. with the participants (industry experts), we have generated the ISM Diagram & MICMAC Analysis.

Objective of our meeting

We expect the following from you:
- Review and validate our results.
- Provide constructive feedback whenever necessary by expressing your point-of-views about individual placement of factors at their respective levels (Level 6 through Level 1). You may also use some real example from your experience in this industry.
- Suggestion for additions/removal for any elements.
- We will need your comment on the usefulness of our results.

Interview methodology

This is to ensure that no area is missed out, we will follow a Q & A session throughout the interview, keeping in mind the objective of the interview. We will start from the most influential level of our ISM Diagram, which is Level 6.

LEVEL 6

Factors: Product type (2)

Based on our information received from other participants (especially drug manufacturers), 'Product type' finds its place at the highest level (Level 6) of our ISM Diagram.

1. Is 'Product type' of the drug is the first factor you think about when it comes to taking a cold chain packaging decision? If yes, why is this factor considered important?

   This is to confirm the placement of 'Product Type' on the most influential level (Level 6).

   Yes, 'Product type' is the first information communicated to us by the drug manufacturer. Each 'product type' has its own requirements and risk. Some chemical drugs are not only temperature sensitive, but they are also limited life.

   The best example would be the distribution of Isotopes, a chemical that deplete itself very moment. In some cases, these chemicals depletion rate increase with the heat etc. So there are so many risk connected with the 'product type' itself.

   The 'product type' gives us a general idea about the temperature requirement of the drug shipment.

   Recently, IATA has developed Chapter 17 that states that each product has a product code. For example, pharmaceutical product has a separate code so

that special care can be taken, meat (frozen meat) has a separate code etc. So the product is also a requirement by regulation.

2. Can a particular 'product type' (drug type) demand special primary, secondary and tertiary packaging that can indirectly change the 'size of the drug shipment'?

   This is to confirm if 'Product type' at Level 6 can influence 'Size and weight of the drug ship' at Level 5.

   Yes, 'Product type' can influence the 'size of the drug shipment'.

   Some 'product type' such as vaccines might be small in size. But due to the primary, secondary and tertiary packaging, the size of its shipment can be much larger than the actual size of the vaccine itself.

   Another simple example where 'product type' can influence the size could be transportation of 'bottled water'. 'Bottled water' are transported in larger quantity than vaccines. The same applies to drug shipments too. Some drug types are transported in larger shipments.

Factor: Time to market (6)

3. One of our participants (freight forwarder) mentioned about situation where the patent of the biologic drug was going to expire. The drug manufacturers wanted to bring their new bio-similar drug (follow-on-drugs) to the market quick as possible. So the freight forwarder used an extremely safe distribution circuit in such case. They choose the safest distribution circuits (routes), avoided connecting hubs wherever possible.

   Have you ever experienced a situation where your client (drug manufacturer) was very concern about the extreme quick and safe delivery for one particular shipment?

   This is to confirm that 'Time to market' factor at Level 6 can influence the shipper's preference on the 'distribution circuit' at Level 3.

   Bio-similar drug manufacturer are in an extremely competitive business. There is always a first mover advantage. As soon as the patens expire for a biologic drug, the bio-similar manufacturer wants to bring their new product first to the market. Therefore they request us to choose the safest and fastest mode of transportation.

   I have an example of how 'Time to market' can be very important and can influence the 'distribution circuit'. When 'Nestle Water', a division of 'Nestle

Group' wanted to introduce one of their new bottled water brands, we used airplanes to bring the water. We never transported bottled water through airplanes, but since Nestle wanted to introduce the product at the right time, we use airplanes.

So yes, the shipper's urgency to bring the product to the market on time can influence the 'distribution circuit'.

LEVEL 5
Factors: 'Size and weight of the drug' (1), 'Temperature range requirement of the drug' (3) & 'Temperature excursion tolerance level of the drug '(4)

1. Do you personally consider these factors when taking a cold chain packaging decision? What is your opinion on the placement of these factors in Level 5 in our ISM Diagram?

   This is to confirm the importance given to these factors in our result, and also to confirm the right placement of these factors in the ISM Diagram.

Of course, these are the key information we obtain from the drug manufacturer. Understanding the nature of the product and the expected volume of the shipment is supposed to be very important factors to consider. Yes, it should be placed in the top priority. Level 5 is fine.

LEVEL 4
Factors: Shipper's concern about the temperature profile of the country of origin and destination

At level 4, the shipper will be more/ (less) concern about the temperature profile of the countries it is transported. Do you agree to the fact that 'Temperature range requirement of the drug' at Level 5 & 'Temperature excursion tolerance level of the drug' at Level 5 can increase or decrease the 'shipper's concern about the temperature profile of the country of distribution'?

If yes, could you share with us a real example of a situation that made you very concern about the temperature profile of a certain country just because the drug's temperature requirements were very demanding?

Yes, these two factors 'Temperature range requirement of the drug' at Level 5 & 'Temperature excursion tolerance level of the drug' at Level 5 can influence the 'shipper's concern about temperature profile of the country of distribution'.

Whenever we distribute temperature sensitive products to South America, we are more concern about of the temperature difference between Canada and Latin America. When it is winter in Canada, it is summer in Latin America. Since our product is temperature sensitive, we perform a small inquiry about the temperature profile of these countries during our planning stage. So yes, the temperature requirement of the product influence us to study about the temperature profile of the country of origin and destination, and sometimes even the countries where we have connecting hubs.

LEVEL 3

Factors: Distribution circuit, Distance to be travelled, supervision and maintenance during transportation, and reliability of the packaging system.

1. Do you think 'shipper's concern about the temperature profile of the country of distribution ' at Level 4 can influence in choosing an alternate 'distribution circuit'?

When we use the term 'distribution circuit', there are two sub-divisions that is:
a) Selection of the air carrier with expertise in cold chain.
b) Selecting a routing according to the terminals the air carriers got in each country.

Certain airlines have more experience, infrastructure, approval and facilities to handle temperature sensitive shipment than others. So first we will select the air carrier capable of handing our shipment depending on their facilities at the country of origin and destination.

Other reasons for changing distribution circuit can be the extreme weather situation in some country, or even because of the lack of infrastructure in certain airports. We have rerouted our distribution circuit several times

because some of the airports in Latin American did not have the facility for temperature sensitive items. Therefore we had to use alternative airports.

So a change in extreme temperature in any of these countries, or lack of infrastructure in the airports, change in the air carrier (due to their better temperature control facilities) can influence the shipper to choose an alternate 'distribution circuit'.

2. Do you think such change of 'distribution circuit' can ultimately increase or decrease the actual 'distance travelled by the shipment'?

   This is to confirm the mutual interdependence between the factor 'Distance circuit' and 'Distance to be travelled' at the same level (Level 3).

   Yes, it can.

3. When you choose a distribution circuit, do you take consideration of the supervision required at each connecting hubs? Our previous interview participants mentioned that they prefer connecting airports where staffs are available for supervision. Can you give an example, if possible?

   Yes, we try our best to distribute these products through connecting hubs (airports) where trained operators are available. For example, our main supplier of active containers is Envirotainer. Envirotainer set its own quality standards for each airport. These active packaging container suppliers will only supply these airports if these airports have qualified to meet their standards. These airports must have trained operator, constant supervision & maintenance and necessary infrastructure. So our concern about supervision and maintenance requirement can influence our decision on the selection of a distribution circuit.

4. Do you think to agree to the fact that the reliable functioning of a particular packaging system is dependent on the distribution circuit selected by the shipper?
   For example, can there be a risk when the temperature of the connecting hubs is -50 degree Celsius, or +50 degree Celsius.

   Yes, the reliability of the packaging system (especially active packaging system) is heavily dependent on the distribution circuit. This includes several factors such as the availability of trained operators at connecting hubs (airport terminal), cold chain warehouse facility for short-term storage instead of keeping the shipment on the tarmac area in extreme weather. We faced several situations where certain air carrier did not have sufficient power charging sockets in their terminal hubs. For example, Air France may be three in their terminal, Luftansa got five in every terminal, but Air Canada got more than ten sockets. Therefore attention should be paid to these small details for the well functioning of the packaging system.

So several factors within the 'distribution circuit' can influence the reliable functioning of the packaging system.

LEVEL 2

Factor: Shipper's concern about the capacity of the packaging system to cope with the unexpected temperature profile

I have read in literature that one of the positive features of an active packaging system is that it provides the greatest flexibility when a shipping system is exposed to a temperature profile different from the qualification temperature profile (Romero, 2013). This feature is unavailable in a passive packaging system.

5. How do you find the placement of this factor in the ISM Diagram

Yes. Firstly this concerns takes only if the shipper is concern about the temperature requirement of the drug shipment. So this concern for the packaging system to be flexible to unexpected temperature profile is driven by the factor 'Shipper's concern about the temperature profile of the country of origin and destination' (5) at Level 4.

Also this concern is influence by the actual 'distance travelled by the shipment' (7) and the 'distribution circuit' used (8). For example, if we are distributing a package to another city in the same country, then we wont be concern about this feature in the packaging system. But if the distance is longer, then this feature of the packaging system becomes important.

6. Will 'shipper's concern about the supervision and maintenance required during transportation' (11) at Level 3 will influence the 'shipper's concern about the packaging system to be flexible to unexpected temperature profile' (10) at Level 2?

No, it won't. Normally, we don't allow the staff at the connecting hubs to change the thermal temperature of the container but we don't want to assign them unwanted duty and task that will create confusion towards the end.

7. How about the factor 'Shipper's concern about the reliable functioning of the packaging system' (12) at Level 3. Will it affect the factor 'Shipper's concern about the supervision and maintenance required during transportation (11)' at Level 2.

No, it is not connected.

LEVEL 1

Based on the 'product type' (Level 1), the drug's temperature requirements, the distance between the country of origin and destination, the distribution circuit, and

several concern about the constant supervision, reliable functioning of the packaging system etc., a packaging decision is made. Basically all the factor from Level 6 through Level 2.

1. Do you believe a shipper will be able to make a decision between an active or passive packaging system at this point after considering all the above factors?

   Yes, the selection of the packaging system is the last decision to be taken so all these factors will be considered.

2. Can you give me an example of the cost differences between an active and passive packaging system?

   There is a big difference between an active and passive packaging system. The actual amount difference will depend on the 'size of the shipment'. Generally, active containers are three to five time more expensive than passive packaging system.

SUPPLEMENT QUESTIONS

1. According to you, do you think there any factor we are missing in our study? If yes, can you explain its importance and its relationship with other factors?

   I think you have included all the factors need for taking such a decision. But you have to give more importance to the compliance part in the 'Shipper's concern about the supervision and maintenance during transportation'

2. Is there any factor that you think are not important in our study that has to be removed?

   I think none of these factors can be removed at all.

3. Our previous freight forwarder mentioned that 'Regulation' was not an important factor at the moment due to the lack of infrastructure in the airport. What is your opinion about this? Do you consider GDP regulation is an important factor you consider before taking a cold chain packaging decision?

   GDP Guidelines are hot topics these days, but it is more used in the warehouses. International shipments are not obliged to follow to these standard all times. But you can include a regulation part in your factor 'Shipper's concern about the supervision and maintenance required during transportation'.

4. How does your company take a cold chain packaging decision? Do the different levels of decision-making in our results (ISM Diagram) matches the way you plan. What are the differences in real life? How do you see the benefit in our result

In real life, we actually consider most of these factors outlined in your ISM Diagram. But don't get a chance to see all of them in such a format. With the help of this diagram, we are clearly able to see the hidden relationship between each factor. This will be useful in have such a diagram for explaining someone new (mainly clients) on how the cold chain packaging decision works.

Thank you for your assistance