Compliant Packaging Solutions in Emerging Markets

Think it's Easy? Think Again

PEER REVIEWED

You might not think that clinical trials and the upcoming summer Olympic Games in London have much in common, but you're wrong. Much like R & D, the logistical planning for the Olympics began years ago and the public investment is estimated at £9.29bn[1]. Sound familiar?

Success in the clinical trials arena is exactly like the athletes preparing to compete in the 110m hurdles. Clinical development is about preparation and execution. All too often having a clear strategy for the distribution of the IMP is left until the last minute. This is like preparing for three years and 355 days for your race only to turn up on the day and not have decided which pair of running shoes you are going to wear, or worse, not having a pair of spikes and running in your wingtips. You will get to the end but you will not win and you will look silly.

A number of recent events bring the safety and efficacy of vaccines into question. No matter how much time and money is invested to discover, develop and deliver life-saving medicines to the world, improper transportation, handling and/or storage can adversely affect patients and damage the brand of the companies that make them.

Two incidents have taken place in what many of us think of as the most developed country in the world – the USA. A study recently released by the Department of Health and Human Services, Office of the Inspector General, examined the Vaccines for Children (VFC) programme, looking at vulnerabilities in vaccine management[2].

The Centers for Disease Control (CDC) and Prevention's programme provides free vaccines to eligible children to provide them with "maximum protection against preventable diseases."

The study measured providers' vaccine storage unit temperatures for a two-week period. Shockingly, 76 per cent of the 45 VFC providers stored or maintained vaccines at inappropriate temperatures for at least five cumulative hours during the period. The study states, "In 2010, approximately 82 million VFC vaccine doses were administered to an estimated 40 million children at a cost of $3.6 billion." This equals $2.7 billion in potentially wasted money, since the vaccines may have little to no efficacy once administered.

The reason for highlighting this report is to recognise that even in the so-called most developed nation, with the most advanced systems to support the healthcare industry, the systems failed.

The report examined vaccines that were in an actively controlled environment i.e. a refrigerator. It did not cover the first 24 hours after the vaccine leaves the distributor and enters and travels through the supply chain. The report also did not examine getting the vaccine to the site, which is significantly more challenging. If 76 per cent of the vaccines were exposed to incorrect temperatures in an active system, what are the chances the vaccines were at the correct temperature during transportation?

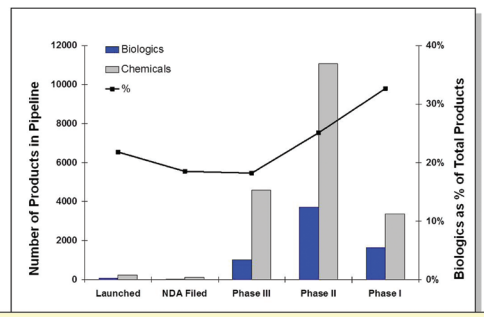
Was it improper storage temperatures, handling or other factors that have led to the recent outbreak of whooping cough in the state of Washington? Health department officials have so far confirmed more than 1100 cases in 2012; ten times as many as the state had at the same time last year[3].

If we are unable to get it right in one of the most developed nations in the world, what hurdles do you face when conducting multi-site studies in emerging markets?

Track Condition – The Situation of Cold Chain in Emerging Markets

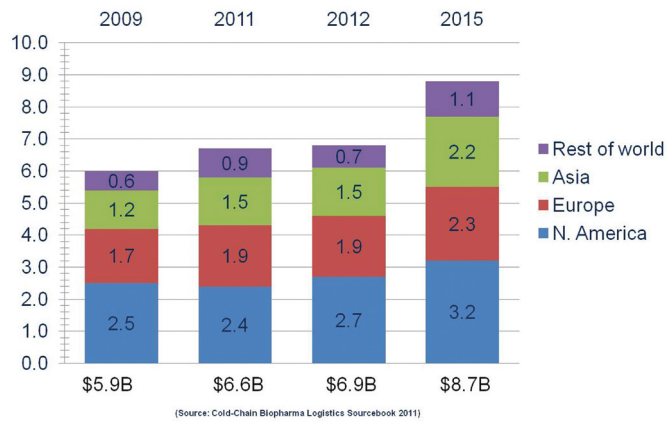
Currently there are 129,099 clinical trials in 179 countries from Afghanistan to Zimbabwe[4].

Between 2011 and 2016, the projected growth of biologics is estimated at $52B[5] from $140B to $192B. It is predicted that by 2016, eight of the top 10 and 27 of the top 50 best-selling global drug products will require 2 - 8°C cold-chain storage and handling[6]. More than 70 % of biologics and 100 % of vaccines are temperature-sensitive.



In the short-term (<3 years) biologics as percent of products launched will be in line with the current trends. However, over a medium to long term a significant increase in biologics activity is expected.

(Source: GlobalData 2011)



(Source: Cold-Chain Biopharma Logistics Sourcebook 2011)

Cold Chain Logistics Growth

Within emerging markets, combining the growth of clinical trials and populations now able to afford western medications, these markets are increasingly importing the latest medications, often biological in nature. The projected growth of cold chain logistics over the next three years is 46 % in Asia alone, far outpacing growth rates in North America (18 %) and Europe (21 %). The ROW (read emerging markets) is expected to grow at an astonishing 57 % (see table above).

Clinical Trials and Temperature Control

With years of research and development invested into the creation of new biologics, how will these new investigational medicinal products (IMPs) get to the patient? The challenge to the pharma industry is transporting these small-batch, high-value, highly temperature-sensitive IMPs to a clinical site for use in a trial. However it does not simply stop at the trial site. For instance, what if the patient is self-dosing at home with pre-filled syringes? How do you ensure patient compliance with temperature management of the IMP with which they have now been entrusted?

Temperature excursions are responsible for the degradation of up to 35 per cent[7] of the world's vaccines. A recently released report by the US Army Medical Materiel Agency revealed that in 1998 more than 200,000 doses of Anthrax Vaccine were compromised due to freezing[8]. It was extremely costly ($5 million in today's dollars) and potentially disastrous. (Since then, the Distribution Operations Center (DOC) was created to manage critical vaccines and pharmaceutical products. Cold chain management processes and procedures now save millions of taxpayer dollars.)

If the same statistics are applied to an IMP that is being distributed to patients, it could lead to issues around patient safety, poor efficacy leading to maligned results, delays in trials, poor recruitment due to lack of product, failure of a trial and increased costs associated with new batch production & distribution. It was as recent as July 2011 that infant patient deaths were attributed to failures in the cold chain[9]. Ultimately, patient safety must come first.

Facing these concerns, the challenges to deliver IMPs to the patient in the optimum condition (having not experienced temperature excursions in transit) are increasing for numerous reasons. Some of those challenges include:

- Increased transit times due to global trials being further afield.
- Lack of reliable supply chain infrastructure within developing nations.
- Environmental challenges with increasingly extreme weather patterns.
- Greater variations in handling due to required use of multiple logistics partners to reach final destination.
- Ever increasing regulatory scrutiny and review of data for transport i.e. increasing use of temperature data loggers.

These challenges and others are certainly pertinent to the development of an IMP, as well as the collection of the sample from the patient and the reliability of the transportation returning it to the lab for analysis.

Will the IMP get to the test site in Siberia before a temperature excursion occurs? Shipping medications in developed countries is made much easier by reliable service providers such as FedEx, UPS, TNT and DHL covering the major developed countries. We know from the major carriers that second day air usually means it will be at its destination in two days.

Once you go further afield, however, transit times become longer and increasingly less controlled. Products may be moved through emerging countries on boats, in cars or vans, by motorcycle, on foot or private plane. Border crossings and customs inspections may cause additional delays to develop.

What if the package is sitting on the tarmac waiting to be loaded on a plane in Mumbai? The temperature control packaging becomes all the more important to keep you from falling before the finish line.

Sizing up the Hurdles – Temperature Control Regulatory Compliance is not Optional

Over the past 10 years, regulatory bodies across the globe have been steadily developing regulations regarding temperature-controlled transportation; however, these regulations vary significantly from country to country and region to region. In addition to the regulatory bodies, including WHO and IATA PGR, standards are being developed by independent bodies such as the Parenteral Drug Association, Technical Report 39 (PDA), United States Pharmacopeia, USP<1079> (USP) and most recently Canada released guidelines for shipping cold chain products, GUI-0069.

Regulations continue to evolve and new guidelines are released on an increasingly regular basis. It puts even greater pressure on trial design and the need to have clinical trial supply chain experts involved as early as possible in the trial design process.

Many packaging and transportation regulations are set by the United Nations (UN) or World Health Organization (WHO) but each country, state, city and town may have additional regulations that apply, for example:

Pharmaceutical Production/Regulation
- FDA Food and Drug Administration cGMP, cGDP, cGLP
- USP United States Pharmacopeia 1079
- Code Federal Regulations 21 CFR 2.11

Transportation Regulations
- IATA International Air Cargo Association, Perishable Cargo Regulations CH17
- International Guidance e.g. PDA, TR39, WHO pre-print
- Regional e.g. EHA
- National e.g. MHRA
- Federal/Local

Supply Chain Protocol – A Clear Strategy to Clear the Hurdles

A clear strategy for the distribution of temperature-sensitive medications is critical to ensure the product is delivered to the patient in optimal condition. Strategy development starts with a few vital questions:
- At what temperature does the drug need to be transported and stored?
- Where does the drug need to go? International/domestic?
- During what season(s) will the IMP be distributed?
- What stability data are available?
- What are the size, mass, and dose format of the drug?
- How is it packaged?
- How much of the IMP can the site receive and store safely in a single shipment?

With these simple questions addressed you can then move onto the next step, route mapping.

Mapping the Routes

Understanding the thermal and time challenges IMPs will experience is critical to making an informed decision as to how to protect them against degradation. The expected thermal exposure that the IMP will experience will define the capabilities required by the temperature control system to provide the necessary level of protection.

When reviewing the routes to be mapped, identify the start points and the expected conditions at point of packaging. This is where mapping of the route must start. An FDA Title 21CFR Part 11 compliant Electronic Temperature Data Logger (e.g. LO-GIC® tags from American Thermal Instruments) should be used to record the temperature to which the package is being exposed.

Mapping Models

There are four ways to gather data for the temperature mapping including "Actual Data", "Averaged Data", "Percentiles" and "Worst Case".

Whichever methodology is selected, it is important to ensure that the methods of transportation meet both anticipated and contingency plans. Additional considerations may include capabilities of the carriers, warehouses and sites to protect the packages from extreme external environments.

Once the data has been collected for each route, time and temperature profiles will be developed against which the packaging will be tested.

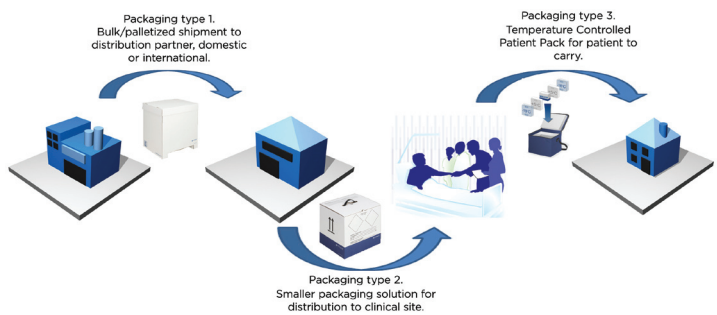
Designing the Packaging Solution

Packaging for IMPs consists of three items: primary packaging (e.g. vial), secondary packaging (vial box, may have branding) and tertiary packaging, which provides thermal, physical and security protection. It is important to remember space/volume costs money to transport, so the most efficient secondary packaging is preferable to reduce both the size and the weight of the tertiary packaging. Increased density of the payload increases thermal performance and stability of the system.

Passive systems range from the very small to multi-pallet solutions. As there are many small and light passive systems, they are often more applicable to the distribution of IMPs than active systems.

Passive systems are well known to shipping personnel and are typically simple to deploy and relatively easy to use. Passive systems contain coolants such as water-based and non-water-based phase change materials (PCM) that ensure a high latent heat melt-freeze transition at precise temperatures. These may be in the form of dry ice, wet ice in brick form, gels or bottle packs. Surrounding all of this will be an insulating material that coolants and payloads are placed into, for example expanded polystyrene, polyurethane, polyethylene or vacuum-insulated panels. Finally there is outer packaging to hold all materials in place and display your company contact details.

Depending on the trial design you may need up to three different packaging solutions to ultimately deliver IMPs in the optimum condition to the patient. Why three?

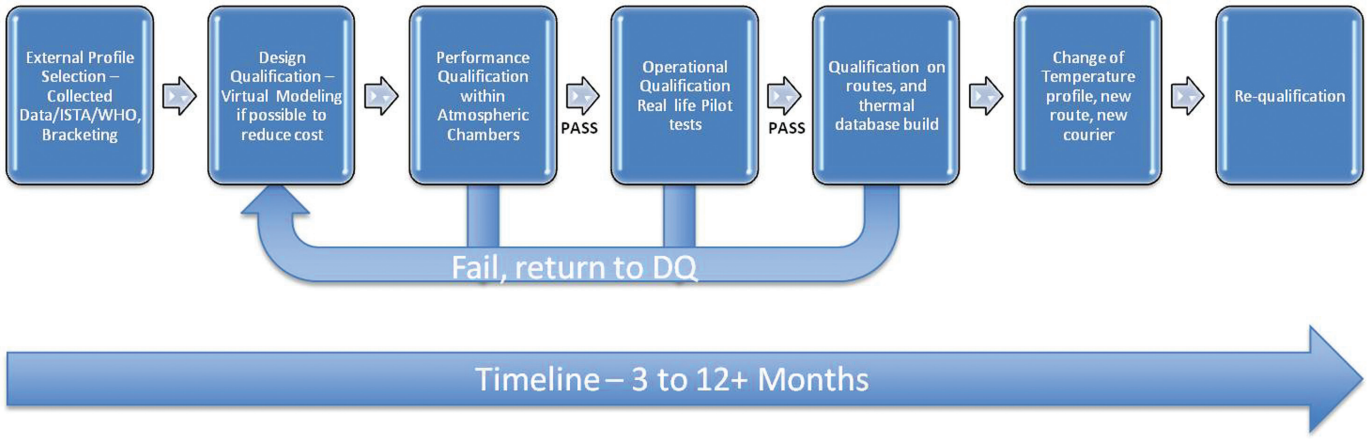


It is important to remember that there is no such thing as a zero-risk shipment. Regardless of how much insulation, PCM and monitoring you place around a payload, there is still a risk associated with shipping since you cannot control the shipment every second of the way. Increased protection may drive up size, and use of exotic materials may increase cost. The challenge is to find optimum solutions for X per cent, dependent on your organisation's appetite for risk. With a risk-based decision-making matrix you will be able to work with a temperature control solution provider to select the optimal system for the payload.

Qualification and Validation Process

Once you have the temperature data, the routes and the number of different systems you require, it is time to start the design, qualification and validation process for the packaging that will ultimately transport your IMP.

Figure 1: Qualification Process



There are three clear steps of qualification prior to validation

- Design Qualification (DQ)
- Performance Qualification (PQ)
- Operational Qualification (OQ).

Prior to starting the design qualification, it is recommended to work closely with a temperature control solution provider to carefully check your profiles and expected exposures. Some solution providers may have thousands of profiles that they may share or at least give clear comparisons. If possible, utilise "Virtual DQ" to reduce cost and time of development. It is also possible that the temperature control solution provider may have "off the shelf" solutions that have already been developed and qualified to meet the expected challenges. However, it is critical that qualification data is not taken as validation, and that any profile provided for a pre-qualified solution is carefully scrutinised to ensure it will stand up to your organisations' challenges.

The design and qualification process map of packaging is shown above: Figure 1 – Qualification Process

Crossing the Finish Line

The selection of proper packaging design is not simple; however the benefits of doing it well may make the difference between success and failure in a trial. It may also be the difference between being first or second to market.

The sooner the process of identifying the solution begins, the sooner you will be able to identify the risks and challenges to the distribution of your IMP.

By selecting and working closely with the right temperature control solution provider you can reduce risk exposure, loss of high-value product, transportation costs, courier white glove costs and integrator courier costs. Most importantly, you will be ensuring the IMP your patient is taking is at its optimal efficacy with no additional risk to patient safety caused by temperature excursions.

Now that you have the IMP safely to the site, all you have to do is get those highly valuable, rare patient samples you have collected back to the lab in optimum condition - simple!

References

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Andrew J. Mills, CEO – Americas: Andrew has been with Intelsius – a DGP Company, for two years, leading the Americas operations in all aspects. Intelsius is a provider of temperature-controlled and regulatory compliant packaging for the life sciences industry. Previously Andrew worked on the clinical development side of the pharmaceutical industry with a global organisation, transporting, managing and banking millions of temperature-sensitive patient samples.
Email: publicrelations@intelsius.com