Simplicity Rules

Despite smaller volumes, proper packaging design and selection for transporting investigational medical products remains a key element in the clinical trials logistics process, and can mean the difference between being first or second to market

Andrew J Mills
at Intelsius

Over the coming years the composition of top-selling drugs will undergo a fundamental change, the extent of which has not been seen before. Simply put, drugs are getting cooler. We are talking about the fundamental shift from traditional small molecule chemical entities to large molecule biologics. This change in the composition of molecules (proteins) drives the need for true temperature-controlled shipments.

Impact of Temperature-Sensitive Biologics on Supply Chain Design

Between 2010 and 2016, the projected growth of biologics is estimated at $62 billion, up from $130 billion to $192 billion (1). 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 to 8°C cold-chain storage and handling (2). The trend is well recognised and is easy to understand; pharma is betting big on biologics.

Much has been written about this transition and why it is occurring. The looming and now present patent cliff has driven major pharmaceutical companies to go on shopping sprees for nimble and innovative biotechnology companies. What has not been discussed in great detail is the effect this has on a supply chain largely built around non temperature-sensitive drugs. A supply chain which, while built around issues such as speed and up-to-the-minute tracking, has not been built around protecting its payloads against highly variable and increasingly extreme environments. On top of this, climate change is starting to challenge our views of what constitutes 'normal' seasonal temperatures.

Clinical Trials and Temperature Control

With years of R&D dedicated to the creation of new biologics as they reach the market, one must question how these new drugs have been tested. How has the investigational medicinal product (IMP) made it to the patient? The cost associated with developing a small batch of IMPs that are biologic in nature runs into the millions due to the high costs associated with small batch production.

The challenge to the pharma industry is transporting these 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 can patient compliance be ensured 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 of the world's vaccines (2). 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, and increased costs associated with new batch production. Ultimately, patient safety must come first. It was as recent as July 2011 that infant patient deaths were attributed to failures in the cold chain (3).

Facing these concerns, the challenges of delivering IMPs to the patient at the correct temperature (having not experienced excursions in transit) are increasing for numerous reasons, and these have been well-discussed in the media. Some of those challenges include:

- Chasing patient populations, leading to increased transit times
- Environmental challenges with increasingly extreme weather patterns
- Greater variations in handling due to required use of multiple logistics partners to reach the final destination
- Ever increasing regulatory scrutiny and review of data for transport, involving steps such as increasing the use of temperature data loggers

Temperature-Control Regulatory Compliance: 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 (PDA), Technical Report 39, United States Pharmacopeia (USP), USP <1079> and, most recently, Canada released guidelines for shipping cold chain products, GUI-0069. Regulations continue to evolve and

new guidelines are released on a regular basis. With this in mind, 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.

Supply Chain Protocol – A Clear Strategy

Having a clear strategy for the distribution of temperature sensitive IMPs several months before a trial begins is critical to ensure the product is delivered to the patient in optimal condition. The strategy development starts with a number of vital questions:

- At what temperature does the drug need to be transported and stored?
- Where does the drug need to go? International/domestic?
- In which hemispheres will the IMP be distributed? North only, South only, North to South, South to North, or both?
- During which 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? Primary and tertiary?
- How much IMP can the site receive and store in a single shipment?
- Is the drug going to be administered on site or will the patient be self dosing (Phase 2 and 3)?

Having addressed these simple questions, it is possible to move on to the next step: route mapping.

Mapping the Routes

As W Edward Deming once said, "In God we trust; all others must bring data." 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 needed by the temperature control system to provide the necessary level of protection. When reviewing the routes to be mapped, it is important to identify the start points and the expected conditions at point of packaging. This is where mapping of the route must start. There is a need to use an FDA Title 21 CFR Part 11 compliant electronic temperature data logger (for example, LO-GIC® tags from American Thermal Instruments) to record the temperature to which the package is being exposed.

Mapping Models

There are four ways to gather the data for temperature mapping; 'actual data', 'averaged data', 'percentiles' and 'worst case'.

In the case of actual data gathering, multiple placebo and real product shipments should be conducted on the routes to be used. During these processes, key factors such as seasonality, deviations from standard operating procedures (SOP) or adverse exposure frequency occurrences should all be explored. Finally, in review of the data, the maximum and minimum exposures should be carefully examined, as well as the duration to these exposures, as this may have a significant impact on any system selected.

The 'averaged data' methodology uses a review of location-based sources such as historical temperature data to develop a temperature route 'map'. As with the actual data gathering methodology, it is important to review global coverage and seasonality. The challenge created with averaged data is that it ultimately leads to 'averaged' exposure, which can lead to potential failure at extreme temperatures.

The 'percentiles' methodology works by reviewing the minimum and maximum temperatures anticipated; in other words, the minimum and maximum temperature of X per cent of shipments. It is then a risk management call to decide what percentage of shipments that have deviations an organisation is willing to accept. Once this has been decided, a time and temperature model can be developed to cover the agreed percentage of shipments.

Under a 'worst case' methodology, routes can be mapped that are expected to have the most extreme exposures. Examples of this may include transporting goods from Chicago to Sydney in December or from Mumbai to Atlanta in August. The challenge is to review worst case scenarios based on seasonality, which ultimately begs the question: are there clear changeover points between the seasons? The issue with the worst case methodology is that collected data is based on worst case scenarios, thereby potentially leading to over-engineering of the packaging solution for the majority of shipments.

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

Once the data have been collected for each route, profiles will be developed

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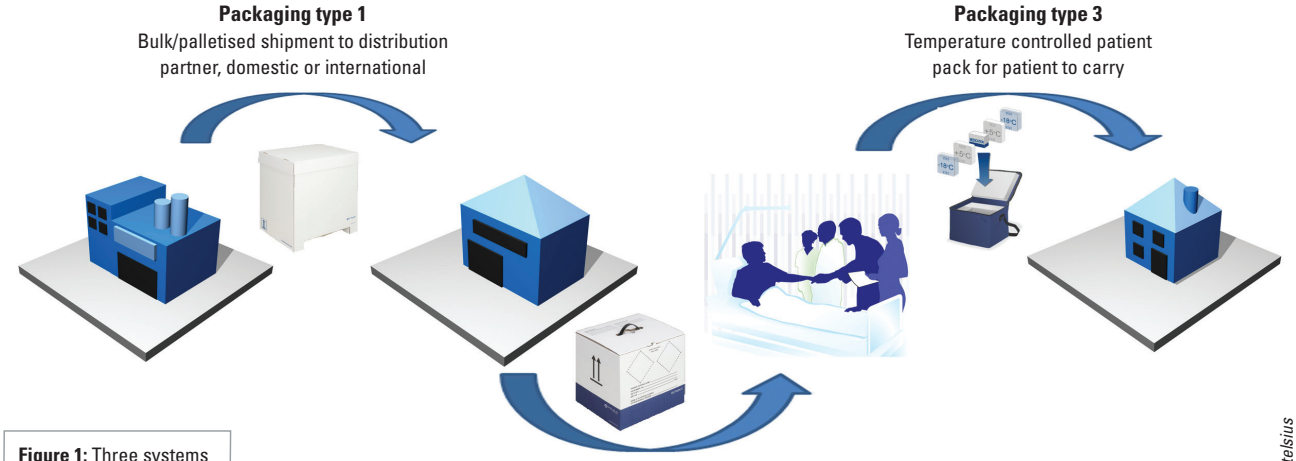

Figure 1: Three systems for trial packaging

Images: Intelsius

against which packing will be tested. The profiles will include both time and temperature to conduct the tests.

Designing the Packaging Solution

Packaging for IMPs will consist of three items: primary packaging (vial), secondary packaging (vial box, may have branding) and tertiary packaging, which provides thermal, physical and security protection. It is important to remember that volume costs money to transport, therefore the most efficient secondary packaging possible is preferable as this will ultimately reduce both the size and the weight of the tertiary packaging. Increased density of the payload increases thermal performance and stability of the system.

Solutions on the market today fall into two categories: active and passive. Active, by the nature of the name, houses active refrigeration or heating systems, much like you would find in your household refrigerator. The methodologies for cooling are the same using vaporisation/condensation cycles in conjunction with refrigerant and compressors. For heating, active systems typically use convection in conjunction with a heater matrix and circulation using a fan. Active systems typically fall into the large pallet or multi-pallet systems, which are designed to either move large palletised quantities of active pharmaceutical ingredients (API) or final commercial product.

In contrast, 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 will be very familiar 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 will be outer packaging to hold all materials in place and potentially display the company's contact details.

Depending on the trial design, potentially up to three different packaging solutions might be needed to ultimately deliver IMPs in the optimum condition to the patient (see Figure 1).

Qualification and Validation Process

Once the temperature data, the routes and the number of different systems are established, it is time to start the design,

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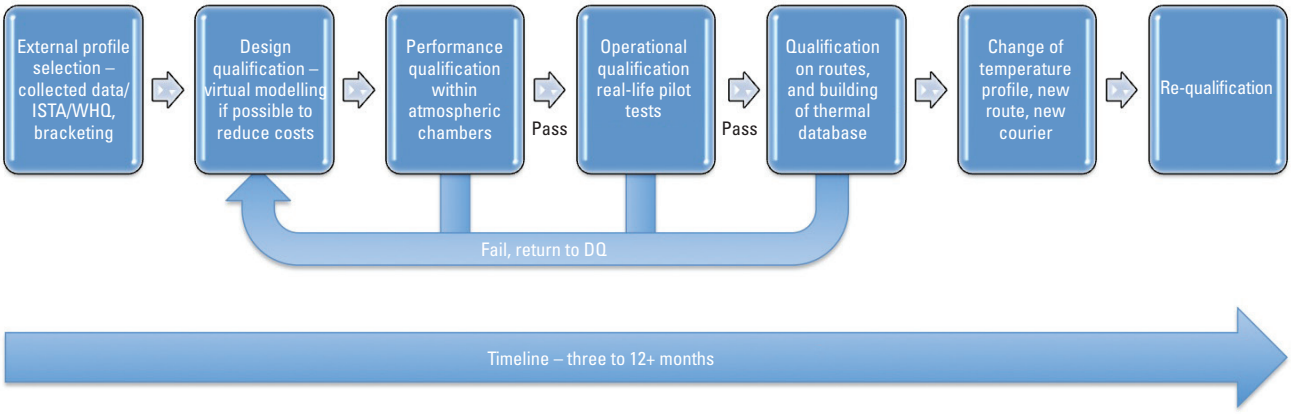
Figure 2: Qualification process



qualification and validation process for the packaging that will ultimately transport the IMP.

There are three clear steps of qualification prior to validation – design qualification (DQ), performance qualification (PQ) and operational qualification (OQ). Prior to starting the DQ, it is recommended to work closely with a temperature control solution provider to carefully check profiles and expected exposures.

Some temperature-control solution providers may have thousands of profiles that they are able to share, or at least point to 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 organisations' challenges. The design and qualification process map of packaging is shown in Figure 2.

Going through the packaging development process, it is important to remember the four S's of packaging design:

1. Simple to prepare
2. Simple to pack
3. Simple to label/mark
4. Simple to ship

Following these rules will help ensure compliance in the cold supply chain. It is also important to remember that there is no such thing as a zero risk shipment. Regardless of how much insulation, PCM and monitoring are placed around a payload, there is still a risk associated with shipping since it is very unlikely that a shipment can truly be controlled every second of the way. Increased protection will also likely drive up size and use of exotic materials and in turn increase cost. The challenge is to find optimum solutions for X per cent, dependent on the appetite for risk. With a risk-based decision-making matrix, it is possible to work with a temperature-control solution provider to select the optimal system for the payload.

Conclusion

The selection of proper packaging design is not simple; however, the path is well-trodden and the benefits of doing it well may prove the difference between a successful trial or a failure. It may also be the difference between being first or second to market. The sooner the process of identifying the solution is started, the sooner you will be able to identify the risks and challenges to the distribution of your IMP. Work directly or as closely as possible with the temperature-controlled solution provider. By selecting the right 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.

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About the author

Andrew J Mills, Intelsius – A DGP Company, is CEO – Americas. Andrew has been with Intelsius for two years, leading the Intelsius Americas operations in all aspects. Prior to Intelsius, Andrew spent eight years working on the clinical development side of the pharmaceutical industry, where he helped establish a global organisation transporting, managing and banking millions of temperature sensitive patient samples.
Email: compliance@intelsius.com