Cool operator

In clinical research, the cold chain is top priority. Through guaranteeing the integrity of investigational medicinal products, study teams can minimise the dangers to their patients and ensure the trial runs to budget and on time. But such in a tightly regulated field, how can pharmaceutical companies ensure compliance and mitigate risk? Genzyme's **Neritan Mustafa** and PAREXEL's **Vince Santa Maria** discuss the pitfalls and the solutions.

The cold chain is a critical part of the pharmaceutical mix. Imperative for ensuring the safety and stability of products – and therefore the safety of patients – a correctly managed procedure is high on the agenda. While this is true for commercial medicines, the issue is particularly crucial in the case of clinical trials.

The majority of today's investigational medicinal products (IMPs) require temperature control, especially in the realm of oncology and large molecule research. Nor is this simply a matter of throwing in a few gel packs: they must be transported in ambient conditions (typically around 2–8°C), making use of such tools as temperature monitoring devices, temperature controlled shipping containers and track and trace technology.

The ultimate aim is clear. Whatever hurdles are faced en route – language barriers, variable climates, complex import and export procedures – the IMPs are required to finish their journey in the same condition they began.

"It's important to execute the physical flows properly without any impact to product quality," says Neritan Mustafa, associate director of GIO supply chain operations at Genzyme. "This requires a strong understanding of the regulatory requirements at a global and local level, as well accounting for the impact of timeline as it relates to the management of the cold chain."

Crucial link

Adopting a cavalier attitude is not an option. While research projects are hugely expensive, cold chain is hardly the place to cut corners. After all, if the chain is poorly managed, the trial's results are unlikely to be accepted, and in the worst case scenario, the company will be forced to discard millions of dollars' worth of drugs.

Regulatory compliance therefore lies in any company's best interests. And although most rules don't pertain to the cold chain per se, the handling and release of the material is subject to stringent quality controls.

"Clinical logistics has become a key ingredient of success in clinical trials," says Vince Santa Maria, senior director of clinical trial materials supply chain services at contract research organisation PAREXEL.

"One of the many challenges is keeping pace with the regulatory evolutions that occur around the import and export of the IMP."

Mustafa agrees. "The cold chain can impact patient dosage and the trial timeline," he says. "We want to ensure that we have an unbroken cold chain that is uninterrupted, and all activities are well managed throughout the chain by all partners to ensure that the products are delivered within the required temperature range."

Treatment in transit

Long concerned with good manufacturing practice (GMP), regulators have been turning their attentions towards transportation processes. This is a place where numerous GxP principles converge:

GMP is a given, but it also includes the rules surrounding clinical excellence, good distribution practice and storage (GCP, GDP and GSP). Cumulatively, these affect every aspect of the chain.

"How are the materials handled, how are the materials packed?" says Santa Maria. "You have to go through testing to ensure that the IMP maintains the temperature, not just in transit but also while it's stored. So if it's held up in customs, it needs to be treated properly, because you want to avoid the risks."

These risks represent a very real possibility. IMPs may suffer from temperature excursion, or worse, expire due to mishandling. If there were no way of telling when this occurs, it could place the end-user in jeopardy. Companies therefore need strategies in place to guarantee their products are not adulterated.

The European Clinical Trials Directive (2004), for instance, specifies that the IMP must fall under the control of a qualified person (QP), who monitors the drug at all stages. This QP is educated in best practice procedures and possesses all the regulatory knowledge necessary to ensure full adherence.

Neritan Mustafa
Neritan Mustafa is associate director at Genzyme, a Sanofi company. His focus for the past 13 years has been understanding the requirements of the global cold chain process, and leading, managing and supporting key activities achieving business excellence aligned to strategy based on robust science, risk management wh

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Then there are rules regarding document management and import compliance. These make sure that the licences are determined correctly up front and that the product receives the proper classification. They stipulate that trade agreements are employed, responsibilities clearly defined in writing and qualification audits imposed – layers of risk mitigation unique to clinical trials.

"This is completely differentiated from the language of commercial products," explains Santa Maria. "Because 99% of drugs used in such trials are going up against a comparator in an existing commercial product, we haven't been there before, and so we have to give it the utmost care."

Of course, while the cold chain is challenging enough if you're moving from city A to city B, it becomes exponentially more complex where an IMP is transported internationally. At present, there is no universally accepted set of standards, and though the last few years have seen some attempts at harmonisation, pharma companies are still compelled to deal with an extensive list of local requirements. For any company operating across borders, it is important to recognise how these rules differ from one country to the next.

"At Genzyme, we ensure that we have a very good understanding of regulatory developments, so we have intelligence throughout, at a global level," says Mustafa. "We turn that into a tangible actionable measurable activity."

Regional guidelines

The World Health Organisation sets out the template, which is roughly mirrored by other regulatory bodies: the Food and Drug Administration in the US, the European Medicines Evaluation Agency in Europe and the Medicines and Healthcare products Regulatory Agency in the UK.

While a comprehensive list of regulations would be beyond the scope of this article, certain rules should be kept in mind. The Saudi Food and Drug Authority, for example, has a regulation entitled 'guidelines for stability testing of active pharmaceutical ingredients and finished pharmaceutical products', which was compiled in 2011. Applying both to IMPs and established medicines, it requires that pharmaceutical ingredients shipped to the EU are accompanied with written confirmation of quality.

Then there is the Canadian regulation, 'Guidelines of temperature control of drug products during storage and transportation: GUI-0069'. Drafted by Health Canada, it aims to increase the efficacy of drugs throughout the nation's health system. The regulation ensures that drug products are transported, handled and stored in the most appropriate way.

It isn't hard to find other examples composed along similar lines. The Czech State Institute for Drug Control has penned guidelines for correct distribution practices of human medicinal products; the Australian court of good wholesaling practice sets out standards for therapeutic goods. The Irish Medicines Board has a guide for monitoring storage and

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temperature conditions for IMPs; Malaysia has guidelines on good distribution practices. Most recently, Peru introduced a set of guidelines for product stability.

While this list may appear overwhelming, the various sets of regulations are perhaps not so dissimilar in reality. "The common denominator is the patient," says Mustafa. "In terms of GMPs and GDPs, there are some subtle differences between countries, but their common aim is one and the same: ensuring that the materials' quality attributes are protected and that the patient is protected too."

Indeed, the main hurdle when crossing borders may not be compliance at all; it might be customs. If any shipment appears to be in doubt, the customs authority will not hesitate to detain that product until the issue has been resolved. And because this storage is uncontrolled, there are no guarantees that they will respect the temperature parameters or even retain the product within its packaging.

It is critical, then, that the pharma company has all its documents in order, ensuring a rapid clearance and seamless cold chain. Here, as everywhere in clinical logistics, preparedness is key.

Another problem that may delay the process is a lack of clarity and transparency. "It's getting more difficult in the EU, especially in countries such as Ukraine where they often change the value of the IMP," says Santa Maria.

"If today client X imports drug A for a commercial value of €100, then when the next shipment of drug A arrives, you write a commercial pro forma invoice to the value of €100. But the customs authority may say no, I just had a shipment come in from client Y and that shipment had a commercial invoice of €200. So it's that constant changing regulatory environment that one needs to keep abreast of, and manage from a global distribution point of view."

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Bearing in mind these pitfalls, it is plain to see that any cold chain solution needs to be carefully planned, tightly controlled and seriously robust. In general, pharma companies would be wise to spend extra on insulating themselves against risk – if you don't factor in all the eventualities, the trial may prove more expensive in the long run.

Supply chain security

At Genzyme, this attitude informs all its logistical processes. Based in Massachusetts, the company focuses on developing and delivering transformative therapies for patients affected by rare diseases. Following its acquisition by Sanofi in 2011, it broadened its geographic reach, and the cold chain issue became more relevant than ever.

"When it comes to ensuring a robust physical flow and maintaining cold chain, we look at technology options," says Mustafa. "Whether it's for packaging technology or monitoring temperature technology, we place emphasis on the importance of supply chain partnerships and collaboration and managing those partnerships with appreciation of the local regulations. We work with folks on the ground in those countries, to ensure we protect our products, ensure dosage of patients and keep trials on time."

These issues are just as salient from the CRO side. PAREXEL maintains good links to the supply chain throughout and endeavours to maintain consistency across all its sites and facilities. It uses electronic systems to its advantage, ensuring its operating procedures are the same in the US as they are in Singapore.

"We track the product from the onset to its final distribution at a clinical site," says Santa Maria. "The operating model we have at PAREXEL gives us the complete visibility and the complete control of the supply chain from cradle to grave."

As trials become more global in nature – especially as they enter emerging markets – the challenges look set only to intensify. Pharma companies will need to be cautious and they will need to be compliant. After all, this is not about encumbering trials with unnecessary bureaucracy. It's about making sure the product arrives in shipshape condition, honouring the safety of participants and furthering the aims of the trial. With regulations continuing to proliferate, study teams cannot afford to drop the ball.

"With clinical trial material, there are risks involved throughout the cold chain, and you have to be aware of those risks to manage them," says Santa Maria. "It's critical for this business."