Good Cold Chain in Clinical Trials

Clinical trials are important vehicles to validate investigational new drugs. Therefore, national and international regulatory requirements for storage, handling and distribution of investigational products are strictly enforced. Any failure during management of study drug is considered non-compliance and could affect the acceptability of the data generated. In addition, that can result in termination of the study and suspension of all research activities at the site. But, most importantly, non-compliance compromises patients’ safety.

Introduction:
The storage, handling, and distribution of temperature-sensitive drugs represent increasingly important components of the global pharmaceutical supply chain. Investigational new drugs (IND) of clinical trials are an important part of the earliest stages of the supply chain.

The basic idea of applying a logistic system in the cold chain is to improve the quality, understood as the fulfilment of user needs with maximum process efficiency.

Biotecnology medicines have experienced strong growth and will continue to drive the development pipelines of the pharmaceutical industry for years to come.

Currently, 15% of the 200 top-selling drugs in the world are of biotechnological origin, and it is expected that by 2025, 25% of drugs will come from this sector. Nowadays, over 325 million people around the world consume biotech drugs.

The “pharmerging” countries account for 9.5% of global sales of biotech drugs – almost 15 billion dollars per year, with an average annual growth of 21.6% between 2007 and 2011, according to an article published in 2012. Pharmerging countries are expected to nearly double their pharmaceutical spending, adding $150-165Bn by 2016. Generic and other products will account for approximately 83% of the increase.

Of the greater than $550 billion (4.7% growth) of pharmaceutical product sold worldwide in 2010, biologics will account for an increased share of spending by 2016, as important clinical advances continue to emerge from research, and patients around the world are treated. Spending on biosimilars will increase from $693Mn in 2011 to $4-6Bn by 2016, which represents 2% of biologic spending ($200-210Bn). In four of the last seven years, fewer than 30 new molecular entities (NMEs) have launched, though this is expected to rebound through 2016, to 32-37 per year. According to the IMS LifeCycle™ R&D Focus™ database for evaluating the market for medicines, more than 31,000 drugs are in R&D, and over 8900 drugs are in active development worldwide. The R&D pipeline remains strong, particularly for products in Phase I and Phase II clinical development. "At the end of 2006 some 2,075 molecules were in development, up 7% from 2005 levels, and up 35% from the end of 2003. In addition, a promising range of drugs is now in Phase II clinical trials or pre-approval stage. Of the total pipeline, 27% of these products are biologic in nature."

Temperature-sensitive investigational products (IP), such as monoclonal antibodies and other biotechnologically produced compounds, need particularly close temperature control during transport and storage. While products are under the control of the manufacturer, the temperature during storage and transport is usually well-controlled within validated and alerted systems.

Given liability characteristics of the IND, due to the fact that they lose immune power from the time of manufacture, it is essential to ensure they reach the user in an optimal state for use, so it is very important to minimise the factors that may reduce or negatively impact their quality.

Given the increased number of global regulatory and standards-based guidance documents issued over recent years, members of the pharmaceutical supply chain are taking notice and making changes to ensure product quality and protect patient safety.

The purpose of this paper is to review the various factors affecting good cold chain management practices for investigational new drugs in clinical trials.

Good Cold Chain: Concept
A cold chain is a temperature-controlled supply chain. An unbroken cold chain is an uninterrupted series of storage and distribution activities, which maintain a given temperature range. It is used to help extend and ensure the shelf-life of products such as fresh agricultural produce, seafood, frozen food, photographic film, chemicals and pharmaceutical drugs. Such products, during transport, are called cool cargo.

Also, the cold chain can be defined as the set of conditions, activities or elements necessary to allow a controlled temperature to retain a biological product or thermolabile product from the time of manufacture to its use in the administration site.

Traditionally, all historical stability data developed for vaccines was based on the temperature range of 2–8 ºC. With recent development of biological products by former vaccine developers, biologics has fallen into the same category of storage at 2–8 ºC due to the nature of the products and the lack of testing of these products at wider storage conditions. The cold chain distribution process is an extension of the good manufacturing practice (GMP) environment that all drugs and biological products are required to adhere to, enforced by the various health regulatory agencies. As such,
the distribution process must be validated to ensure that there is no negative impact on the safety, efficacy or quality of the drug substance. The GMP environment requires that all processes that might affect the safety, efficacy or quality of the drug substance must be validated, including storage and distribution of the drug substance.

Importance of Cold Chain
It is essential to maintain an adequate and constant temperature in each of its component links, to ensure perfect preservation of the products. Therefore, it must minimise thermal and critical control points, because an inadequate thermal alteration can cause accumulative alterations, so at the end of the chain, the drug may be in an altered state.

Cold Chain and Clinical Trial
Clinical trials are being run on a global scale, and in some cases in markets with less than ideal logistic infrastructure. The complex clinical supply chain creates a challenging distribution environment because of the shipping of large volumes of refrigerated kits to patients worldwide. Given the great number of clinical sites, there is increased complexity for maintaining product quality and mitigating the risk of thermal excursions. The product distribution process should be monitored to obtain a set of data showing that it is correct and secure. Any failure must be properly documented, investigated and corrected to avoid the same in future shipments. If there is failure, influences in the quality, safety or efficacy of the product could lead to its withdrawal from the clinical trial to ensure patient safety.

Personnel who work with temperature-sensitive investigational products include speciality couriers, contracted depots and shipper manufacturers, improving the performance of the supply chain and building a more robust clinical trial distribution process. One of the most significant factors affecting the potency of medicinal agents is the ability to maintain them in controlled environments. Therefore, maintaining the chemical and therapeutic integrity of investigational medicinal products poses special cold chain challenges, since clinical trials require multiple shipments to many study sites worldwide.

Temperature excursions during the storage, handling or distribution of temperature-sensitive clinical trial material pose significant safety and financial risks. A cold chain failure may lead to four key risks:

1. The patient could be administered an unsafe product
2. The lack of compliance with global regulatory standards requirements can increase liability
3. Thermal variability can lead to inconsistency of results between and within batches
4. The shipment can be rejected by the quality department, thereby leading to costly delays – increasing the complexity of trial management.

The pharmaceutical developer/manufacturer pays attention to temperature and/or physical conditions which may affect the good storage and good distribution practices (GSP/GDP) of their materials/products during clinical trial.

Four primary regulatory trends have been identified:
1. Accountability for the cold chain ultimately resides with the manufacturer, but responsibility is shared across all supply chain partners.
2. Increased oversight, management, and control of environmental conditions across the entire supply chain.
3. Increased importance of temperature control and monitoring.

Geoffrey Glauser, former Director of Logistics at Fisher Clinical Services, stated: “FDA is focusing more on the supply chain control of pharmaceuticals or biologicals ... The establishment of that control needs to start with clinical materials, the associated known stability data for the drug, and how the manufacturer has maintained the environment throughout the entire supply chain.”

In some cases (e.g., in early phase studies), the need for control is even greater for IND in clinical trial, because the stability of IND may not have been fully established. “The distribution of clinical trial materials to different trial sites can present additional risks to these materials.”

The sponsor should ensure that the investigational product(s) (including active comparator(s) and placebo, if applicable) is characterised as appropriate to the stage of development of the product(s), is manufactured in accordance with any applicable GMP, and is coded and labelled in a manner that protects the blinding, if applicable.

The International Conference on Harmonization (ICH) Topic E6 “Good Clinical Practice: Consolidated Guidance” 1997 is a commonly referenced industry document. This guidance was developed by an ICH Expert Working Group and received input from regulatory authorities. ICH E6 has been adopted by the regulatory bodies of the European Union, Japan, and the USA.

Section 5.13 “Manufacturing, Packaging, Labeling, and Coding Investigational Product(s)” – 5.13.2 of ICH E6 – states: “The sponsor should determine, for the investigational product(s), acceptable storage temperatures, storage conditions, (e.g., protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, if any. The sponsor should inform all involved parties (e.g., monitors, investigators, pharmacists, store managers) of these determinations.” Furthermore, Section 5.13.3 states: “The investigational product(s) should be packaged to prevent contamination and unacceptable deterioration during transport and storage.”

Section 5.14 “Supplying and Handling Investigational Product(s)” – 5.14.3 states: “The sponsor should ensure that written procedures include instructions that the investigator/institution should follow for the handling and storage of
investigational product(s) for the trial and documentation thereof. The procedures should address adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from subjects, and return of unused investigational product(s)...” 5.14.5 states: “The sponsor should take steps to ensure that the investigational product(s) are stable during the period of use.”

While the above documents provide helpful guidance, all applicable local requirements and regulations need to be reviewed and considered. For example, Cuba Good Clinical Practice section 6.13 “Manufacturing, Packaging, Labelling, and Coding Investigational Product(s)” – 6.13.2 states: “The sponsor should determine for the investigational medicinal product(s), the acceptable storage temperatures, reconstitution fluids and procedures and devices for product infusion if any. It should inform all parties involved (monitors, investigators, pharmacists, storekeeper) of these indications.” Section 6.13.3 states: “Investigational medicinal products should be packaged to prevent contamination and unacceptable deterioration during transport and storage according to the current regulatory requirements about medical management.” 15 Section 6.14.4 states “The sponsor should take steps in order to ensure that the investigational product is stable during the period of use.”

In addition, The Department of Clinical Trial’s Pharmacy (Center of Molecular Immunology) has a documental system; it includes INS-2042, INS-2073, INS-3004, INS-3005, LCH-2018, PNO-1097 and Reg-2448. The INS-2073 “Packing and Transportation of Investigational Product(s)” is about how investigational product must be packaged by clinical trial and by investigation site, and the conditions of transportation. 21

The checklist (LCH) - 218: “Control of the product at the investigational site” has some important aspects that should be checked to ensure a good management handling of IND at the investigational site22. This checklist was developed according to the regulations of Center for the State Control of Drugs, Medical Equipment and Devices (CECMED) for the handling and use of the IND at the investigational site.23

The previous examples are just a few of the existing regulatory and guidance-based standards, and they provide a solid background on good cold chain management practices related to the storage, handling, and distribution of clinical trial materials.

Cold Chain at the Investigational Site:
Once the investigational product (IP) is delivered to the investigational site, and depending on the availability of a pharmacy and the GMP training of staff at the investigational site, the storage and handling of the IP are more often subject to errors and mishandling.

Cold chain investigational products are often subject to deviations during storage at the investigational site due to, for example, defective refrigerators, refrigerators not designed to keep a temperature range of +2-+8°C, or simply having the refrigerator door open for too long. When a deviation has been identified and reported to the sponsor, the qualified person responsible for IP of the clinical trial (usually the clinical pharmacist) is often the final addressee to comment on the deviation and its impact on the quality of the IP stored in the refrigerator concerned.6

The temperature measured by the temperature sensor can be considered representative only if the fridge has been qualified and a temperature range of 2-8°C is kept at all storage positions within the fridge. Additionally, the temperatures measured and documented are only suitable for interpretation if the temperature sensor has been calibrated initially and subsequently at pre-defined intervals.

A close daily monitoring with, e.g., calibrated min/max thermometers should be performed and documented. The staff of the investigational site should be made aware of temperature-sensitive IPs, and trained on proper handling and storage. They must also be aware of the importance of informing the sponsor immediately of any deviations which have occurred.6
Conclusions

It is necessary to develop an internal documentation system as well as multi-communication standards and protocols to track information across the supply chain. These systems would monitor equipment status, product temperature history and custody chain, etc. These help ensure that the IP is safe and effective when reaching its intended consumer. It is also important to have a complete chain of custody for the entire lifecycle of a product, so there is documented evidence as to who had control of it throughout the lifecycle of the product, up to the final users.

The growth of the biopharmaceutical market, combined with the complexity of the clinical supply chain and global regulatory environment, require that all supply chain partners are aware of appropriate regulations, local requirements, protocol of study, and industry best practices related to the storage, handling and distribution of temperature-sensitive products. Regulatory guidance and inspectional trends demonstrate a focus on good cold chain management practices. All partners should have the common goal to demonstrate a focus on good cold chain management practices. All partners should have the common goal to ensuring that each patient and site received the correct medication at the right time and in the right condition.

References

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