Is Your Temperature Data at the Clinical Site out of Sight?

We have all heard that the journey is as critical as the destination. However, in the world of clinical supplies, did you know that most temperature excursions occur at clinical sites during storage and not during transit? This gives a new perspective to how we view the criticality of the destination. The higher volume of excursions at clinical sites is not due to poor performance by the site personnel or due to the length of time the clinical supplies are held at the site. It is really more kudos to the world of distribution service providers that have upped their game with new products and technology over the past couple of years.

With an ever-increasing number of temperature-monitored drug products shipping globally, sponsors and CROs are constantly facing challenges on how to effectively and efficiently collect and analyse end-to-end temperature data of their investigational medicinal product (IMP). Collection of temperature data throughout the clinical supply chain is something that is widely recognised as being of the utmost importance to protect the integrity and quality of the drug, thus ensuring the safety of the patient.

Temperature data in the supply chain can be categorised into two distinct groups:

Transit Temperature Data

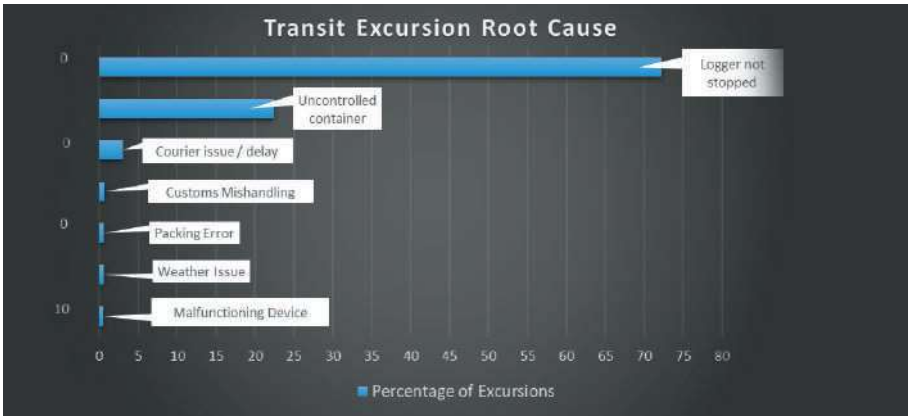
The first group of temperature data to consider is transit temperature data recorded during shipment to a CMO, to an in-country depot or to the clinical site. As regulatory bodies are asking more questions around the management of temperature data during transit and asking for proof that shipments arrived in good condition and within specification, the majority of sponsors and CROs will have a process in place to manage and collect temperature data recorded during transit. It is now widely understood that sponsors and CROs should collect all temperature data to ensure there have been no excursions during transit rather than just collecting alarmed device data.

Site Storage Temperature Data

Site storage temperature data is the second group of temperature data that sponsors and CROs need to collect. This collective term covers temperature data recorded when the drug is at site with a CMO, at a depot awaiting onward shipment, or when the drug is being stored at the clinical site ready for dispensing to a patient. As CMOs and depots are audited facilities, sponsors and CROs can be sure that any adverse temperature events are reported to them through the CMO/depots validated processes. It is common, however, for sponsors and CROs to struggle to monitor and manage temperature data at the clinical site. Clinical sites are recording temperature in a variety of formats with many completing manual daily temperature logs which makes accessing records difficult. Without this visibility, the capacity to identify and adjudicate excursions, uphold compliance and safeguard patients becomes restricted.

Many sponsors and CROs may ask why it is necessary to have visibility of both transit and site storage temperature data. This is of course to make sure that drug product has been shipped within labelled conditions and continues to be stored within labelled conditions once it has arrived at its destination. Sponsors understand the importance when it comes to keeping drug within labelled claims rather than shipping on stability data only. Complete transparency of temperature information throughout the supply chain ensures that there is visibility on any excursions that have happened either during transit or at site. Without gaining access to all temperature data, it is impossible to be sure that there have been no excursions throughout the supply chain and therefore this could leave the patient at risk of receiving drug that has been stored outside the labelled conditions.

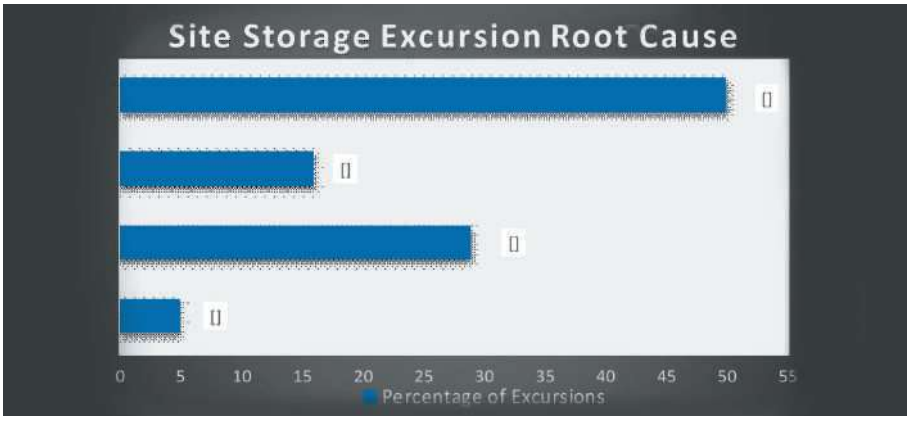
Contrary to popular belief, it is not the distribution phase of a temperature sensitive drug's lifecycle that poses the greatest risk of excursions. The transit element of the supply chain has a definitive beginning and an end; the temperature device is started and placed in with the shipment and is stopped when the shipment arrives. Furthermore, advancements in phase change shippers and temperature device technology have resulted in a decrease in transit excursions. The reality now is we see the majority of these reported are not actually true transit excursions and potentially measures could have been taken to avoid them. Graph 1 shows an overview of the number of transit excursions reported to a CMO documenting the root cause of each excursion.



Graph 1: Transit Excursion Root Cause, Source: Survey results obtained from internal Almac data

From the graph it is clear that over 90% of excursions reported could have been prevented as the root causes were 'logger not stopped' and 'uncontrolled container' utilised. True transit excursions account for a very low percentage which therefore proves the transit element of the supply chain is well controlled and we have access to data that can drive changes and improve excursion rates going forward.

When we look at site storage excursions reported to the same CMO (Graph 2), we can see the challenges that sites are experiencing are much more complex in nature and often the temperature data alone is not conclusive.



Graph 2: Site Storage Excursion Root Cause, Source: Survey results obtained from internal Almac data

Site errors such as incorrect placement of the temperature device and product mishandling are common reasons for site storage excursions, as well as the challenges that sites can face when it comes to equipment malfunctioning. With much more varied and complex root causes of site excursions, the risk of excursions is highest during storage at clinical sites. Site storage is where temperature-related data capture and analysis processes designed to manage and mitigate risk are typically least robust. Sponsors and CROs need to find new methods of capturing what is happening at site and gain better access to the recorded data, thereby giving them better control over these excursions.

Before we look at the processes for capturing and analysing site temperature data in an efficient manner, we need to review the challenges with managing temperature data at the clinical site. Very often, we see clinical sites running multiple protocols for the same CRO or sponsor and recording and reporting information individually, which takes considerable time and duplicates efforts. We also see, in reality, having a method to centralise temperature data collected at site, even when there are processes in place to try and do so, has been difficult to achieve in a timely manner. Frequently CRAs are tasked with reviewing site temperature data when they visit with a clinical site. The challenge with this practice is the visits may only occur a few times throughout the year and it becomes difficult to track how sites are performing in between visits. If CRA visits are infrequent then consideration also needs to be given to how long the window of risk is between the CRA visits and what the outcome would be if an excursion happened within that period but was not reported. Another challenge for sponsors and CROs is having a centralised place to review transit and site storage data. With a major focus around the collection of transit temperature data, there are a number of solutions in the industry to help streamline and automate the centralisation of transit temperature data. However, there are limited solutions when it comes to combining both transit and site storage temperature data in one place for review.

One of the other major challenges is asking the site to complete tasks beyond what they typically carry out within their defined processes. This can be a difficult obstacle for the sponsor/CRO to overcome as it could potentially increase the burden on the clinical site. In a recent survey, it was found that the vast majority of clinical sites globally are recording temperature data at site with over 92% of respondents stating that they were recording data. This is a positive place to start because at the very least, sites are recording the information that sponsors and CROs need to access. An element which links closely to this is the method the site is using to record temperature data. In the same survey, it was discovered that the majority of clinical sites globally prefer to record temperature data at site using a manual recording method. With sites also utilising building management systems, USB site devices and Bluetooth/app technology, there are a variety of different methods being used by sites globally and this needs to be considered when managing site temperature data.

Sponsors and CROs, along with their CMO partners, need to be able to present solutions to the site that help encourage compliance with collecting temperature data from site at defined time intervals. The first area to look at is the return of temperature data. As already noted, sites are recording temperature data at their storage locations in a variety of different formats, and sometimes multiple different formats within the one site. To ensure compliance, it is recommended that sponsors and CROs adopt the method that the site is currently using to capture temperature data rather than forcing them to adopt a new process that suits the sponsor or CRO. The only way to manage streamlining return of all of this information in different formats is to implement a solution/process that can accommodate return of temperature data in multiple formats, and this should be considered by the sponsor/CRO at study setup. Accepting the format that the site is currently using to record temperature data should help compliance with returning the information to the sponsor or CRO.

If possible, sponsors and CROs should also consider a site storage data collection process which allows

linking of temperature data across all their protocols. This ensures a streamlined process for the site where submission of a temperature record per storage location is only required once, and this information is shared against CRO/sponsor protocols as applicable. This helps to reduce the burden on the site even further and should help increase the compliance of the site by reducing the workload.

A large number of sites also prefer to have the sponsor or CRO provide an appropriate site storage device at the start of their protocol. This could indicate that the site is not comfortable in making their own assumptions regarding which type of monitoring device is suitable. If a site is running multiple protocols for multiple sponsors, each providing their own specific device, then the site management of all temperature devices will become very difficult and cumbersome. This could potentially affect compliance with sites returning temperature data and should be considered across the industry in terms of sites having generically programmed site temperature devices and allowing them to share temperature data across sponsors and CROs.

As long as temperature-sensitive drug continues to be shipped and stored globally, there will be increased focus on sponsors and CROs from regulatory bodies to monitor each point in the supply chain and have access to the temperature data used to support dispensation of drug product to patients. Sponsors and CROs should make every effort to have an effective temperature data management process in place to ensure visibility of all temperature data from the supply chain whilst encouraging clinical site compliance. It will not be possible to have a "one size fits all" approach globally across different clinical sites and temperature ranges. These are factors that need to be considered carefully when implementing an efficient management process. Access to temperature data that is accurate and reflects the state of the drug will continue to be a topic for discussion and sponsors and CROs are encouraged to take action.

Sarah Smyth

Sarah Smyth graduated from Queens University Belfast with a BEd in Business Studies. After graduating, Sarah gained a wide range of experience working in the clinical diagnostics industry, especially around solutions regarding shipping temperature sensitive product in challenging climates. Sarah joined Almac in 2016 and has worked with a large number of Pharma and Biotech companies initially in developing proposals to fulfil packaging and distribution needs, aiding in the successful delivery of a range of clinical trials. More recently, Sarah has worked closely with clients to understand the challenges they face with distributing temperature sensitive drug product and advising on the best solutions to implement for efficient management of temperature data on a global scale.

Heather Bogle

Heather Bogle graduated from Queens University Belfast with a BSc in Chemistry. She joined Almac in 2001 and has worked with a wide range of Pharma and Biotech companies, from small specialist providers to multinationals, to manage supply chains across the full range of sponsors and trial designs. Heather has first-hand experience in managing the supply chain for studies across the globe with temperature sensitive products. She has expert knowledge on the challenges with temperature management throughout the supply chain and extensive experience developing creative, efficient and robust solutions.