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WHITE PAPER

Understanding 2015 Data Integrity Regulatory Requirements for Temperature Controlled Pharmaceuticals

we prove it.

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The UK Data Integrity Guidance states raw data must be «legible and accessible, retained in the format in which it was originally generated, throughout the data lifecycle». From a business perspective, we know that raw data generated in the supply chain is valuable to understanding its performance – if handled correctly. But how? It's more efficient to ensure raw data is connected to the original data record, which is certainly done using a relational database. If you're manually processing flat files, it can be resource intensive to review numerous spreadsheets for example, and more subject to error when archiving and storing paper records or flat files.

That is just one example how there are different ways to set up your temperature monitoring program. Each way may offer unique business benefits and options for data integrity. Data loggers, types of files, raw data, and a database – all work hand in hand to create a cohesive process-driven system. As you establish your monitoring program, consider how to achieve both compliance and your business needs … by making the right choices.

The FDA recently announced it will begin more inspections related to FDA 21 CFR Part 11; the regulation concerning electronic records and signatures to be trustworthy and reliable. Without a plan in place to handle electronic records in every GMP department in a pharmaceutical company and their partners; those companies risk receiving Warning Letters, or worse 483s from the FDA for non-compliance. The FDA is also holding a series of workshops in 2015 in India on Multicentre International Data Integrity. FDA has stated this is not just a problem in India but an industry-wide concern, noting issues around quality control inspections, equipment qualification, and training in all GMP environments.

Likewise this year, the UK MHRA created their own guidance and regulatory expectations for «GMP Data Integrity Definitions and Guidance for Industry», released in March. Data integrity has become a major regulatory concern following discovery of fabricated / manipulated data in laboratory chromatographic data systems. Regulatory authorities are now asking where has the data originated from, what type of electronic proof certifies authenticity such as e-signatures, and have those systems been properly validated for their intended purposes. The new Data Integrity guide covers all areas, machines and equipment that generate data in manufacturing and supply chain functions for pharma.

Similarly, the Pharmaceutical Inspection Cooperation Scheme (PIC/S) Guidance on Good Practices for Computerized Systems in Regulated GxP Environments echoes the same requirements. This has recently been adopted in Japan, another major market, in addition to the US and Europe.

Then there is GAMP 5. It is also very clear that data quality and integrity is of high importance; «Patient safety is affected by the integrity of critical records, data, and decisions, as well as those aspects affecting physical attributes of the product.»

Definitions and Interpretations for the Cold Chain

It's clear the new UK regulatory guidance reflects other national regulations and industry standards from around the world, including the FDA. But what do these data requirements mean for your temperature controlled pharmaceuticals?

Raw data – must be legible and accessible, retained in the format in which it was originally generated, throughout the data lifecycle. Paper is acceptable. However the MHRA guidance states «In the case of basic electronic equipment which does not store electronic data, or provides only a printed data output, the printout constitutes the raw data».

Archive – MHRA says «Archive records should be locked such that they cannot be altered or deleted without detection and audit trail.» In cold chain, you need to make sure your temperature and shipment records are files that cannot be changed after generation from the device. Whether you print the file for record keeping or upload to a database, the original record needs to be kept intact. Ideally with the raw data integral to the original files.

If your data logger generates a PDF report, you should understand that the suitability of a PDF file for archival preservation depends on options chosen when the PDF is created. These options include whether to use encryption, and whether to preserve additional formation from the original document beyond what is needed to print.

ISO 19005-1 underlines the importance of PDF/A, a specialized PDF file format for regulated industries. It was created to address growing need to electronically archive documents to preserve over extended periods of time to ensure they could be retrieved and rendered with a consistent and predictable result in the future. This is important for complex supply chains if you have multiple destination sites, including remote geographies that can change over time. You don't want destination sites have to install software updates to ensure they can open a PDF file generated from a data logger. Instead by using a data logger that generates a universal PDF format, like PDF/A, it doesn't matter what version of Adobe they have or what version was used to create the file. Think of Microsoft Word updates over the years; if someone sends you a *.docx* created in «new» Word, how can you read it if you have «old» Word? You have to re-save it as *.doc* (old format) or install a docx reader on top of old Word, but losing functionality. With PDF/A, no matter how many updates your Operating System runs, you can still read those files and they will retain functionality and compliant archiving for long term storage.

«Increasing demands for traceability and cold-chain integrity are making data systems more complex and configurable with increased risks of inadequate data integrity. Companies should consider a risk assessment of data associated without the supply chain considering raw data for both cold-chain and logistics aspects.»
Ian Holloway, MHRA, May 2015. Leading Minds Seminar

Electronic audit trail required by 2017 – GMP audit trails are metadata that are a record of GMP critical information, which permit the reconstruction of GMP activities. As already described, it is cumbersome to have paper records of your shipment data. However, for some organizations who haven't convinced management yet to upgrade, it's their only option. The MHRA guidance says this is acceptable, if the paper audit trail can demonstrate also changes to the data. However, they will expect by end of 2017 companies to have an integrated electronic system or validated audit software.

Computerized system user access – Regulators are asking … who has access to your data? Can you prove who amended a record or created a supplementary report? In setting up a temperature monitoring for your cold chain, who has access to add data to your central repository or database? Hundreds of people at various destination sites such as hospitals, clinics or depots; or is database access limited to certain number of admins or product owners? How does that data get into the central document system, manually entered by hand; or securely emailed in?

Relational Database vs. Flat Files

The new MHRA guidance explains relational databases are inherently more secure, as the data is held in a large format which preserves the relationship between data and metadata. This is more resilient to attempts to selectively delete, amend or recreate data, compared to a flat file system.

Beyond compliance, relational databases offer greater business advantages. Compiling spreadsheets and running formulas can take a lot of time. Paper files, however compliant they may be, are cumbersome to use for processing excursion reports. When all data is housed in a central system, running regular reports and analysis of your shipping performance is a no-hassle activity, and in turn creates business value in the form of greater efficiencies and cost savings to your logistics and quality operations.

Building in Data Integrity

As the number of products and shipments grow for many pharmaceutical manufacturers, they are looking for better ways to manage extensive shipment and temperature data. Most often this means transitioning to a streamlined, comprehensive data monitoring system. Having a central repository for temperature data covers several regulatory requirements at once. A validated database ensures the records are original, there is a permanent archive in place and in some systems, keeps the raw data intact with the original record.

Because these central repositories are custom, requiring configuration and supplier involvement, following GAMP 5 guidance ensure a system is validated for its intended purposes. GAMP 5 explains «Procedures for specification, configuration, verification, and operations of the system should be agreed between the regulated company and the supplier and be documented in the appropriate plan. Procedures adopted may be those of the regulated company or from the supplier QMS».

Therefore if you're considering adopting a new data monitoring system for your temperature controlled supply chain, GAMP 5 Good Practice Guide explains that the supplier's Quality Management System (QMS) should:

1. Provide a documented set of procedures and standards
2. Ensure activities are performed by suitably competent and trained staff
3. Provide evidence of compliance with the documented procedures and standards
4. Enable and promote continuous improvement

«… It should be possible to associate all changes to data with the persons making those changes, and changes should be time stamped and a reason given. Users should not have the ability to amend or switch off the audit trail.» MHRA Data Integrity Guidance 2015

If compared to the 2015 MHRA guidance, the UK definitions focus on components of the system recommended to be built in to ensure data integrity. These include: access to clocks for timed events; user access rights which prevent data amendments; access to raw data for staff performing data checking activities. It later states, «… system design should always provide for the retention of full audit trails to show all changes to the data *while* retaining previous and original data. It should be possible to associate all changes to data with the persons making those changes, and changes should be time stamped and a reason given. Users should not have the ability to amend or switch off the audit trail».

Different Temperature Monitoring Approaches and Technology – Are You Compliant?

Technology	Situation	Compliant or not? Questions to ask vendors.
Indicators	Low cost, go / no go decision	To be compliant, you need an original record. So if you're using an indicator, does it offer more than an visual reading? Can you print out a record, or upload to a database? In those two cases, you would be compliant.
USB data loggers	USB data loggers produce electronic records, but how can you prove they retain integrity?	MHRA requires data record to be proven original by «preserving the integrity (accuracy, completeness, content and meaning) of the record through the data's full lifecycle». If you use USB data loggers that have been validated according to USP 1079 or EU GMP Annex 15 to ensure prevention of manipulation, and can produce a validation report; you will be compliant in preserving the integrity. For example, one system on the market produces a PDF/A that by GAMP 5 design, cannot be manipulated. Some data monitoring systems also use measures such as a unique check sum identification that is original to each logger and it's PDF; proving its source and originality. **Ask:** How does the monitoring system prove that files are original and unaltered? Is there a system of checks and balances that is easy for the user to understand and follow?
Database or hosted document management system	How can you ensure your database vendor has a solution that fits your regulated activities?	**Ask:** How does the system ensure that each data logger file is uploaded with the correct metadata? **Ask:** What performance checks does the system have to ensure each file is unique, and that no duplicates are present? **Ask:** Does the hosted document management system conduct automatic integrity checks, or will it accept any document? **Ask:** Under what guideline is the system developed, and how is FDA 21 CFR Part 11 compliance ensured? **Ask:** How are files and metadata stored?

Regulatory Inspectorate's Advice

In May 2015, ELPRO and Envirotainer hosted a Leading Minds Seminar in New Brunswick, NJ. Ian Holloway from the MHRA presented how the new Data Integrity rules affect temperature control professionals. He stated «Increasing demands for traceability and cold-chain integrity are making data systems more complex and configurable with increased risks of inadequate data integrity. Companies should consider a risk assessment of data associated without the supply chain considering raw data for both cold-chain and logistics aspects.» He presented a series questions to challenge pharmaceutical manufactures to ask themselves:

- ☐ Is your raw data retained and secured against unauthorized changes?
- ☐ Do you have adequate metadata – data-about-data?
- ☐ Would you detect unapproved changes?
- ☐ Do system users have appropriate access controls and defined user rights?
- ☐ Is your data attributable, legible, contemporaneous, original, accurate, complete, consistent and enduring?
- ☐ What risks do you have from Cloud storage/services?
- ☐ Are any spreadsheets fully validated and secured?

Concerning Data Quality and Sources: Lessons Learned

During the seminar, Holloway provided actual inspection examples of how temperature data was questioned in a number of pharmaceutical supply chains (companies names kept anonymous).

Case Example 1

A temperature controlled medicinal shipment was being transported in India using temperature controlled vehicle, then sub-contracted to self-employed haulier. The refrigeration unit switched off to reduce fuel costs. The problem was first detected on arrival in the UK.

Learning Point: Transport arranged by head office commercial team (higher rank and importance than local staff at the production site). How good is your knowledge of the local cultural aspects of your partners?

Source: Ian Holloway, PowerPoint, Leading Minds Seminar May 2015, New Brunswick NJ. Disclaimer – This vehicle was undergoing repairs by the roadside. There is nothing to suggest that this vecicle was carrying pharmaceuticals at the time the picture was taken. Althought the company in Case Example 1 exists and is real, ColdEx is not the company. This image is an example solely to show the unusual «Piping Hot» slogan on the side of the vehicle.

Case Example 2

After a shipment reached the UK, the data loggers were sent back to the origin site in a third-world country for reading. This resulted in questionable data, making it difficult to decide when data logger had been stopped with reference to receipt of product in the UK. Slow timelines mean that it was too late to carry out a meaningful investigation.

Learning Point: Prompt local reading is much more reliable and can mean that evidence is still obtainable to facilitate investigations if there are suspected deviations.

Case Example 3

An airfreight shipment from India to the UK consisted of 11 pallets but only two data loggers had been used to monitor transit temperatures. This is not adequate to ensure that none of the nine unmonitored pallets had not been exposed to unacceptable temperatures in a different hold of the aircraft. Ref EU GMP Guide: 1.4(xvi).

Learning Point: No documentation was available to indicate which two of the 11 pallets have been monitored. 2015 MHRA regulatory expectation is now one data logger per pallet; not per shipment. This was the same company at both ends of the route – systems and communication should have been better!

Summary

Without a doubt, there are a number of regulatory requirements and industry standards around the world that govern how you handle data in a GMP. Many of the principles are the same, as outlined in this paper. However, most Quality and Logistics professionals are not also trained in IT. That's why it's critical to work with experienced data partners when considering a data monitoring system for your temperature controlled products. Choose a data monitoring partner who's system can help you comply with regulations and ensure integrity of your valuable data – *the state of being whole, entire, undiminished, or in perfect condition*.

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