Adapting to an Everchanging Regulatory Landscape

Compliance in regulated laboratories isn't static; the rules and guidance are constantly evolving to improve standards and the quality of drug products. However, the areas of non-compliance found during regulatory inspections typically remain unchanged, with the same issues being observed from year to year. The bulk of the non-compliance issues arise from breaches of basic principles of Good Manufacturing Practice and Good Laboratory Practice (GxP), requirements relating to procedural control, documentation standards, a lack of scientific investigation, training, maintenance, qualification and validation of both hardware and software.

The regulatory inspection program was impacted on a global level during the COVID-19 pandemic as inspectors were no longer able to travel overseas and visit regulated companies to carry out conventional site-based inspections. As a result, regulatory authorities around the world quickly developed virtual inspection processes that utilised a combination of video technology to inspect facilities and interview staff while documents and supporting information were shared across secure digital channels.

Many regulated companies still use paper-based systems that rely on physically sharing documents and information with inspectors during a face to face, on-site inspection. The paper-based approach can cause significant difficulties when being inspected via the new virtual inspection process, which is heavily reliant on having digital documents and information readily available. Having to scan paper documents and information into digital formats is a time-consuming process and provides significant delays during a virtual inspection that may impact the final outcome. A number of regulated companies used the pandemic as an opportunity to update their Quality Management System (QMS) and move away from paper-based systems to digital workflows to future-proof their quality operations.

From an inspector's perspective, there's a preference for digital data as it contains additional meta data, information relating to how a piece of data or result was acquired, processed and reported. Digital data provides greater visibility of the activities performed during the analysis phase and can better determine whether any data manipulation or falsification has taken place.

Regulatory authorities around the world have not reverted back to site-based inspections even though COVID-19 restrictions have been relaxed and travel routes to foreign countries are becoming increasingly available. They are instead relying on their global network and collaboration with other regulators via Mutual Recognition Agreements (MRA). An MRA enables a regulator in one country to accept an inspection performed by a regulator in a different country, who has been assessed and confirmed to operate to equivalent inspection standards. In the future, therefore, site-based inspections may only be deployed for "high-risk" companies with either a poor compliance record, or for novel products that are possibly first to market and may be performed by a local regulator. It is highly likely that regulators will continue to use virtual inspections for "low-risk" companies that are overseas, enabling the regulator to maintain their inspection program but focus resources on high-risk areas.

Intended Use Instrument Qualification

The United States Pharmacopeia (USP) <1058>,[1] which covers Analytical Instrument Qualification (AIQ), was updated in 2017 to include more detailed requirements for instrument qualification as well as connecting the requirements for software validation and data integrity.

Many regulated companies operate an Original Equipment Manufacturer (OEM) policy that relies on the instrument manufacturer to provide a qualification program. Following the changes made to USP <1058> in 2017, inspectors now want to see companies performing a detailed risk assessment around how instruments will be used as part of their GxP product test program. The "intended use" of the instruments will then define how they should be qualified to ensure the "range of use" is tested during the qualification. As a result, two companies can be using the same instrument, but they will be analysing different products and using different methods, meaning the qualification requirements will be different. Many regulated companies are now providing their User Requirement Specifications (URS) to OEM and service vendors to request custom qualification programs to meet their specific requirements and range of use.

Software Qualification and Validation

Modern software platforms are designed to be flexible and used across many different industries for various purposes. In today's modern laboratories, a single instrument can have a variety of applications, but regulated companies expect software to be designed for their specific use to minimise compliance risk and protect the integrity of the data. Software platforms do have the ability to meet the latest regulatory requirements but that depends on the configurable options selected by the end user – compliance therefore comes from choosing the right configuration and proper use.

There is a common misunderstanding within regulated industries about the difference between software qualification and software validation. Qualification checks that the functionality of the software is working correctly once installed, and it is at this point that end users often think their software is validated. Validation, however, is a second process; testing to show that the software has been correctly configured, with all the technical and security controls, and is suitable for the

regulated workflows to safeguard the integrity of the data. The confusion around these two very different steps means that companies often omit the final validation stage, resulting in significant compliance risks and GxP data potentially not being considered valid.

Data Integrity

With the increased use of electronic data, it is imperative to have systems and processes in place to ensure the accuracy, consistency and safety of your data. Using digital workflows within these modern software platforms puts you in the safest position from a regulatory risk perspective. Digital workflows provide the necessary safety net for you to defend the validity of your electronic data and associated results that you may have used to bring drugs to the commercial marketplace. Many companies now perform data integrity risk assessments on software platforms being used within regulated laboratories, changing the software configuration and revalidating to close any data integrity gaps. It is these steps which will minimise future inspection risk.

Evolving Regulations

Ten years ago, regulated companies only had to prove to an inspector that they had run a qualification on their instrument. Now they need to have a customised qualification programme, based on their specific user requirements and intended use. Laboratories need qualified and validated software, which must have data integrity controls built in. The result is good control around instruments and software and data security, but there could still be questions around methods being run on specific instruments.

Analytical Quality by Design

USP reviews its general chapters on a five-year rolling basis so the next revision of USP <1058> is expected towards the end of 2022.

In January 2022, USP published a stimulus paper in Pharmacopeial Forum edition 48[1] titled "Analytical Instrument and Systems (AIS) Qualification, to support Analytical Procedure Validation over the Life Cycle". This paper is currently under review by the USP expert committee to determine whether the draft chapter will become official later this year.

The major change to the USP <1058> chapter is the inclusion of Analytical Quality by Design (AQbD) to link in with USP <1220>, another USP general chapter covering The Analytical Procedure Lifecycle that was first issued in 2016.

The <1058> chapter has evolved significantly over the last 15 years. The 2008 revision only included general information relating to instrument qualification. The 2017 revision provided an expanded focus for instrument qualification to include the need to perform risk assessments and intended use qualification as well as covering requirements for software validation and data integrity. The next focus for the 2022 revision is to include AQbD requirements to ensure that the methods used for GxP testing are robust and fit for purpose.

Many regulated companies have problematic methods which made it through validation processes but prove to be less reliable when used regularly as part of GxP test programs. Inspectors want visibility of these problematic methods during regulatory inspections and are now expecting to see trend data relating to method performance. The trend data that the inspectors seek is available as digital data (meta data) within the software platforms that you are using to acquire, process and report GxP results. If an inspector observes that you have partial sequences with failed System Suitability Testing (SST) within your software, it will be a red flag that your method is not robust and may be impacting the quality of the data it produces. This may lead to an inspection observation requesting that the method be re-developed and re-validated to improve its robustness.

Compliance isn't Optional

Maintaining a compliant and effective laboratory is getting increasingly complex. Moreover, compliance isn't optional – failures are penalised, and non-compliance behaviour can have a negative impact on the credibility of a company. For example, warning letters are published in the public domain on various regulated body websites such as FDA Data Dashboard, Health Canada and the Eudra GMDP database.

Meeting complex regulations isn't just top of the agenda for a select few sectors like pharma and biopharma, which may come to mind first for being traditionally regulated. Emerging industries across food and beverage, environmental and lifestyle sectors are also being subjected to increased regulations.

It is therefore essential for regulated laboratories of all sizes to work with trusted partners that have the right experience and tools to help them optimise workflows while also maintaining the highest possible compliance levels. This approach will help minimise inspection risks.

REFERENCES

1. https://www.agilent.com/cs/library/whitepaper/public/compendium-LED-compliance-USP1058-5994-1134en-agilent.pdf, visited on 16 March 2022

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