LIVE SYSTEM ASSESSMENTS WHY DO THEM?

by Rachel Carmichael

I have a vivid memory of a certain "pre-exam stress" period as my old production site prepared for my first regulatory inspection in the early 1990s. The theory, even then, was that we would be *continuously inspection ready* but that didn't stop us from wanting to ensure that we presented our best face to the inspectors.

We would pre-run the obvious tasks, including ensuring that we could create a summary report of the last two years' worth of deviations encompassing all departments and all the stages of the events. This is dynamic data in an ever-changing database. Depending on how you requested the search, certain events could be included or excluded. Our endeavor was to make sure that all events were there.

After nearly 10 years in a production environment I became an Inspector for the MHRA and spent nearly 11 years seeing how other companies handled their inspections. The vast majority had done some preparation. Normally the first part of the inspection will include a review of the deviation system. The companies where the staff knew what they were doing would prepare a summary report of the last two years' worth of deviations and we would select a small number of reports to review in detail. Not long after I'd started, I had cause to become rather suspicious of the prepared reports and so I became rather more interested in the search criteria that had been put into the databases to define this so-called 'comprehensive report'. I started to ask for the reports to be rerun on that day, not necessarily to be reprinted, but certainly to look at any differences. On more than one occasion I found that certain departments had been omitted. Was that intentional? Only the hosts can ever say.

REGULATORY BACKGROUND

The idea that a company can "manage" an inspection or an inspector is either overly optimistic or at the very least naive. In Europe, where the production and storage sites are licensed, the refusal of an inspection,

or failing to respond to inspectors' requests, can result in the license being taken away surprisingly quickly. I found that it was a very rare event for me to have to take out my warrant card and remind people of their legal obligations to comply with the inspection process. That said, I never had to do it twice.

Since 2012 the U.S. has had stronger legal grounds to deal with people that *"delay, deny, limit or refuse an inspection"* through the Food and Drug Administration Safety and Innovation Act (FDASIA). In the guidance that was issued in October 2014 to accompany that Act, companies should not limit access to company records from the FDA: Section V, sub part C, Limiting Access to or Copying of Records.

If found to be in contravention of these requirements a company may have their product considered adulterated. For U.S.-based companies this may take some time to play out in the courts but for overseas companies an import alert can be placed very quickly. The FDA procedures governing the review of electronic records are published in chapter 5 of the FDA Investigations Operations Manual (IOM) available on the FDA website.

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Particularly of interest is section **5.3.8.3.2 – ELECTRONIC DATABASES AND QUERIES** which highlights the concern around the accuracy of such transient queries in dynamic data from an ever-changing database, and instructs inspectors:

> *"You must assume the query logic is not validated and take appropriate action to ensure the data is accurate and no data has been accidentally omitted due to a programming logic error."*

Clearly, relying on printouts from such databases is an inherently weak approach and inspecting directly in such systems is far more efficient. This same section clarifies that "Reviewing data contained in electronic databases is generally most effectively accomplished with the use of a computer" and gives the following guidance when it is necessary to access a firm's data during an inspection:

- Oversee the firm's personnel accessing their system and have them answer your questions
- Request the firm run queries specific to the information of interest
- Request the firm provide the parameters used to generate the data
- Request the firm to copy the data to electronic storage media

As more and more companies and organizations moved to comprehensive electronic quality management systems (eQMS) (such as QPulse which is extensively used within the UK NHS), the need to inspect directly in the electronic systems increased. These systems hold all the procedures, all the training relating to those procedures and all the elements of the pharmaceutical quality system that you would expect to see; deviations, change control, risk management, audit program.

QUALIFICATION REQUIREMENTS

Clearly the systems should be qualified. Many organizations contract out this activity but the responsibility for its suitability for use within our type of environment stays with the user. While there may be an installation and operational qualification from the provider, the performance qualification should be done by the organization. It should ensure that your system works as intended within your network and environment, and meets compliance requirements including those for data integrity. During the operational qualification the procedures for use should have been developed and these should be used during the performance qualification. Many companies develop good procedures for how to use the system but are tempted to take a more flexible approach with regard to the administration of the system and make statements like "refer to the administration team" without actually being clear as to what they are meant to do and how.

POTENTIAL OUTCOMES

Sensible companies will also have specific information regarding reporting. A number of systems have predefined reports and also allow the company to run ad hoc reports. The failure to control this was evident at one of my inspections where the organization had not realized that the predefined reports were present in their comprehensive eQMS. When we ran the reports, live, during the inspection, we produced metrics significantly different from the official metrics for the site. The live reports identified that very few staff had conducted the required confirmation for training in the procedures. Furthermore, the reports identified that large numbers of documents were considerably past due for review and that deviations were being re-scheduled constantly with, effectively, no oversight. In less than five minutes we had established the lack of control of their operation and that management review was fundamentally flawed, being based on incorrect (sanitized) data.

PREPARATION – YOUR ESSENTIAL TIPS

For companies with such systems, recognize that one day your inspector will want to audit live in the system. It is common practice now. To prepare for such live system assessments, your own self-inspection program should adopt the same approach.

In preparation, consider the following:

- Know which of your systems are likely to be inspected in this way – eQMS; any of the individual quality systems such as your deviation system, change control, complaints and training; and shop floor electronic systems and laboratory systems

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> Make sure you've identified staff who are capable of hosting such an exercise. You need the super users to be able to demonstrate the system and the reports. You do not want people hosting that are unfamiliar with the capabilities of the system.

  - *Remember that, even for custom systems, you have no idea what your inspector knows.*

> Conduct internal audits live in the systems. Make sure your routine challenges and checks challenge the way in which the systems could be looked at. It is possible that the system administrators have not had to face inspectors, so these practice events are key.

> Ensure that you understand the automatic reporting built into the systems. Be prepared to explain any potential differences that the live system reports may generate compared to your official metrics.

If you're not used to going directly into electronic systems remember that your inspectors can be very familiar with large numbers of different systems, have no fear about looking at another electronic system and adopt approaches that are very open and so cannot be "managed".

WATCH OUT!

Make sure that your IT department understands it may have to support the site during inspections and that this is a company priority. I once had a surreal experience where the IT department (in a very large organization) declared that they were a corporate group and were not required to assist a site and the person that could have helped went home!

USEFUL RESOURCES

A site that has good control of its data integrity will be in a stronger position to withstand this type of inspection and your starting point should be the ***PIC/s guidance (currently Draft v3), Good Practices for Data Management and Integrity In Regulated GMP/GDP Environments.***

Looking more holistically, in 2016 the ***ISO 9001 Auditing Practices Group issued Guidance on Electronic Documented Information Systems.*** This document gives "general guidelines for the conduct of audits of management systems that are either fully electronic-based or have a high degree of documented information in electronic media". Although it is intended for people who have wide-ranging experience of these types of audits, it was written to be accessible to those who do not and should be suitable for internal audits. The document takes you through planning for your audit, review of documented information, on-site operation activities and auditing the control of electronic documented information. In addition, it touches on resources, electronic communications, multisite management systems and auditor competence.

CONCLUSION

It's important to recognize that a live system assessment inspection is going to happen. Preparation is key. Understand your systems and reporting capabilities, your key staff and their likely capability when under the full focus of inspectors, and above all practice and challenge your systems – do not have blind faith! We are here to help if you would like an external challenge of your systems. Contact us at **pharmamail@nsf.org**.

Further useful resources are available in our resource library – **www.nsf.org/info/pblibrary**:

> Webinar:
  How to Install a Data Governance Process from Ground Zero

> White Paper:
  Data Integrity – A Closer Look

> Webinar:
  Regulatory Perspectives on Data Integrity

> Case Study:
  How to Correct an Unexpectedly Difficult GMP Inspection and Prevent a Relapse

ABOUT THE AUTHOR

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Ms. Carmichael is eligible to act as a Qualified Person under the provisions of EU Directives and is a member of the Royal Society of Biology. She has wide-ranging experience of inspecting against European Good Distribution Practice and Good Manufacturing Practice requirements in the UK, China, India and the U.S. to meet the associated quality standards for medicines (non-sterile and aseptic production, including radio pharmaceuticals) and the blood industry.

Her areas of recognized expertise include:

- Manufacture and packaging of oral solid dosage forms
- Good Distribution Practice
- Good Manufacturing Practice
- Blood industry: Blood establishments, hospital blood banks and plasma collection sites
- Data integrity
- Pharmaceutical law

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