Data Integrity in the Pharmaceutical Industry: How Bruker BioSpin can help **.

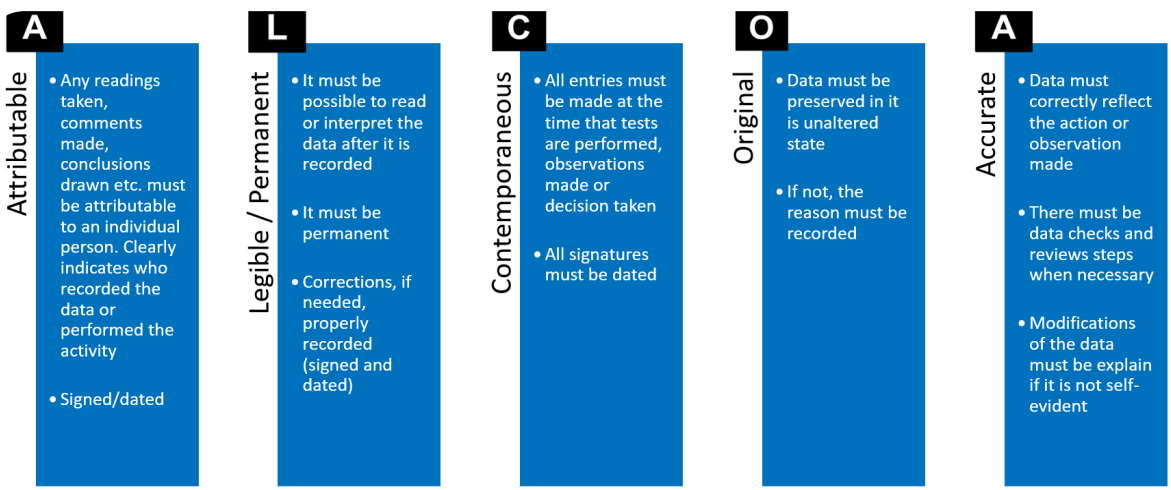
Ian Clegg PhD (ian.clegg@bruker.com)

Bruker BioSpin

Whenever data is generated, processed and analysed, it is important that it is done in a manner that is consistent with the principles of data integrity (DI) so that the data, together with any conclusions drawn from it can be used with confidence.

Within the pharmaceutical industry, the basic principles of DI are encapsulated by the acronym ALCOA (see Figure 1) although these in turn are based upon sound scientific principles: for example, they help to ensure that data has been obtained correctly by suitably qualified personnel using calibrated and maintained instruments and that the data has been stored in its raw form as well as with the metadata that unambiguously describes how it has been processed.

Figure 1



** This paper was first published in the form of a newsletter that was published by validnmr. com; link https://www.validnmr.com/blog/ (accessed 12Jan2021)

[1] https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters. (link accessed 08Dec2020)

The principles of DI have special status within the pharmaceutical industry due to the fact that adherence is mandated by the industry regulators but primarily because the underlying reason is that non-adherence can lead to the loss of efficacy of pharmaceutical products and/or can cause their safety profile to be compromised: both these possibilities could have serious negative consequences for patients.

Those working within (and with) pharmaceutical development and manufacturing continue to have a strong focus on DI and this is especially true of the industry regulators. Clear evidence of this is to be found through analysis of warning letters issued by the American Food and Drug Association.[1] This information, which is in the public domain, has been analysed by many interested parties to uncover general trends and themes. It is noted that in the period 2013-2020, there have been over 130 warning letters issued to companies throughout the world that contain at least one negative finding about DI. In these warning letters, some details have been redacted and they show some variability in terms of detailed focus, but it is very clear that DI is still a "hot topic" as far as the regulators are concerned. An interesting warning letter, published in 2020, was issued to a company site in the USA (see the inset to the right) – it seems clear that a series of DI problems were evident at that site at the time of the inspection.

The analytical techniques that are most frequently used in pharmaceutical development and manufacturing are those based on separation science and vibrational spectroscopy and these techniques are often cited in the FDA warning letters.

NMR is not widely known for being used in Pharmaceutical Development and Manufacturing environments (i.e. those where GxP is applicable[2]). Actually, the technique is used quite widely and in order for that status to be appreciated by a wider range of end users, whitepapers on this subject have been published.[3,4]

These describe multiple applications of NMR to pharmaceutical development and manufacturing, ranging from raw material acceptance, to in-process controls and final product release. They cover a range of molecular types and sizes, including biomolecules and the NMR methods can be based on 1D experiments (^{1}H and ^{13}C) or 2D experiments such as HSQC.

Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records (21 CFR 211.68(b)).

Your firm lacked controls necessary to assure the integrity of electronic test data. Specifically, you failed to implement sufficient controls to support the integrity of your data and to ensure that only appropriate individuals had administrative rights.

Notably, a demonstration performed during the inspection revealed that the computer operating the (b)(4) spectrophotometer (ID: L-563) was not secured such that data files could be deleted without the knowledge of your quality unit. This instrument was used for finished product release and stability testing for several drug products.

Your response was inadequate because it failed to include a comprehensive review of all laboratory instruments to determine whether all user roles are appropriate. You acknowledged that your software was not working as intended and you lacked the necessary knowledge or experience to troubleshoot the issue. You noted that you are pursuing remediation for the (b)(4) spectrophotometer.

Your response was insufficient because it lacked a retrospective assessment into how system vulnerabilities may have impacted data integrity.

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture.

See FDA's guidance document Data Integrity and Compliance Drug CGMP for guidance on establishing and following CGMP compliant data integrity practices at https://www.fda.gov/media/97005/download.

In response to a series of customer requests for assistance, Bruker BioSpin has developed a series of GxP Readiness "kits". Each kit consists of an integrated set of components such as qualification protocols, a computer system validation protocol, certificated reference standards as well as various supporting documents (e.g. manuals and certificates).

The latest kits also include software components critical to comply with the current data integrity expectations. The "GxP Readiness kit NEO", for example, has been designed from the outset for compliance with the objective of making the DI capabilities of NMR equivalent to, or better than, those available to the competing and more widely used analytical techniques.

[2] GxP: Good Laboratory Practice or Good Manufacturing Practice

[3] "NMR under GxP in Drug Development and Manufacturing" by Kerry Hughes, PhD and Ian Clegg, PhD. Whitepaper from Bruker BioSpin 2020. https://www.bruker.com/nc/products/mr/mr-in-pharma/instrument-qualif ication.html (link accessed 08Dec2020)

[4] "Successful commissioning of an NMR system for a GxP environment: details of a modern and efficient approach to achieving compliance" by Valentin Poirier, PhD and Ian Clegg PhD. Whitepaper from Bruker BioSpin 2020. (copy available from the author)

The principal examples of this are:

1. For reasons of enhanced security, data is held in database since that is the accepted standard in this sector.

2. Experiment submission can be performed via a web interface, ensuring data integrity i.e. Log-in and log-out occurs without compromising acquisition and attribution.
3. A variety of user role types are supported, including NMR centric roles such as an analyst, a system administrator and a QA specialist.

The second and third points above illustrates a general theme for our software design i.e. the need to support diversity. Our customers require the software to be used in a variety of different ways to suit their prevailing Standard Ordering Procedures (SOPs) and local preferences and thus we must be able to accommodate such choices. It is therefore possible to submit experiments remotely if required but it is also possible to submit NMR experiments in the more "traditional" manner i.e. via TopSpin or IconNMR.

To be clear, the software system has been designed for compliance and there are multiple features that support the principles of ALCOA and that cannot be switched off or otherwise avoided e.g.:

1. Once activated during commissioning, the audit trail functionality cannot be switched off and the audit trail itself cannot be edited.

2. Digital signatures can be added at various points

3. User authentication occurs via a two-step process to ensure that only authorised users have access to the spectrometer, and to the permissions that have been assigned to them.

From the perspective of the user, there are other enhancements that are less about compliance and more about convenience, for example:

Sample submission is via a sequence of forms that queue the sample into the automation system. These forms are configured based upon the local requirements and details, and these also go through an approvals process. This aspect is delivered by the Mestrelab package "Mdrive" (Figure 1), a key component of the kit.

Figure 2

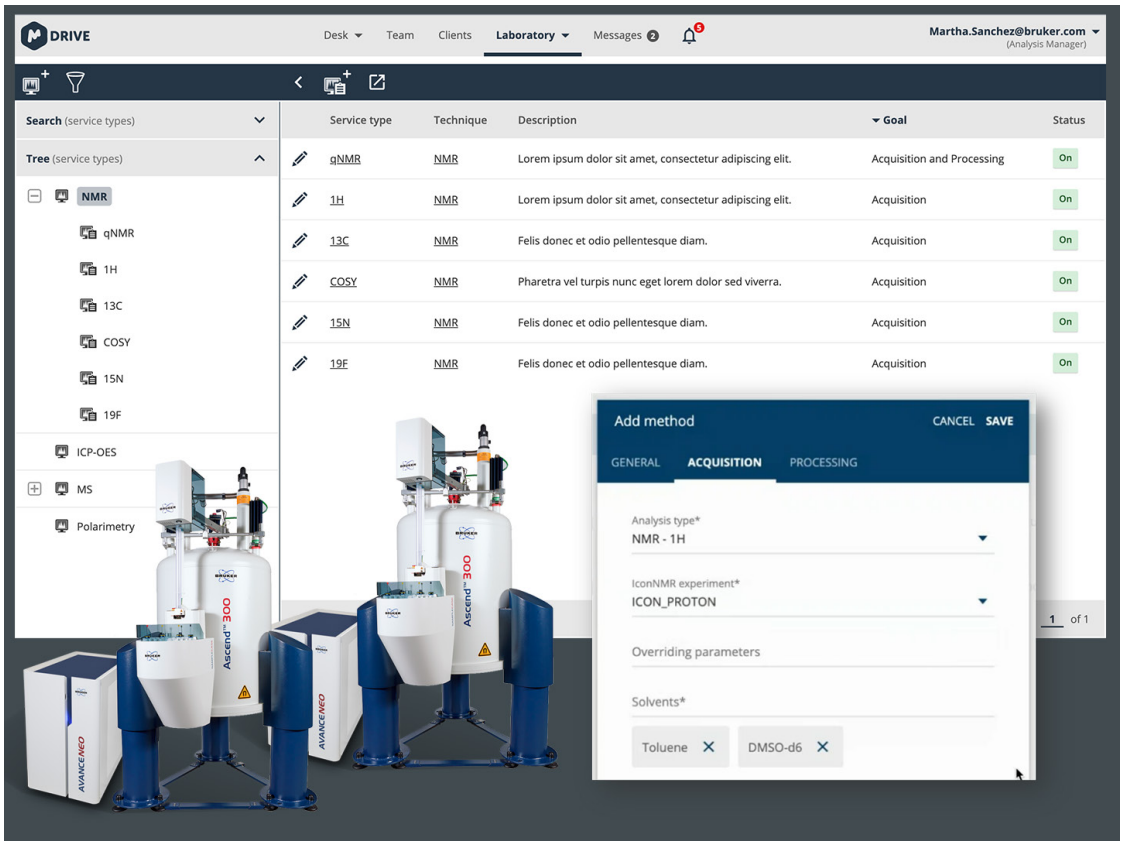


Figure 2. Mdrive example screen shots

As a further example of how we have designed the system to be as convenient to use as possible, the audit trails have also been set up so that they can be searched and evaluated both easily and quickly using a variety of criteria such as user, date range, project name, activity type (Figure 3). The results of such searches can be exported to e.g. pdf format and be readily used by QA or for audit reporting.

In summary, this article describes some of the Bruker BioSpin perspectives on DI and it also discloses several features that help to ensure that customers are able to achieve and maintain compliance.

Figure 3

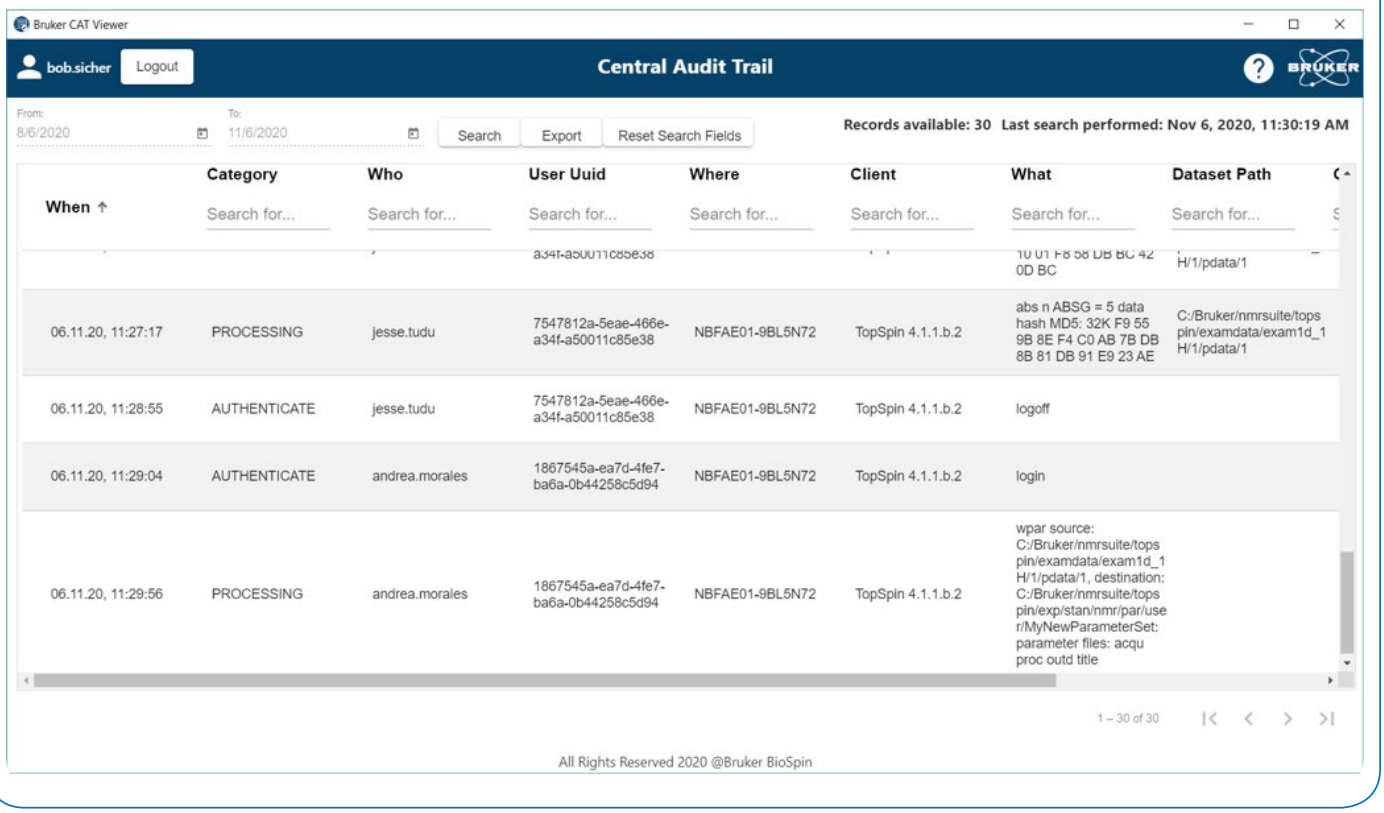


Figure 3. An example central audit trail

Bruker BioSpin

info@bruker.com
www.bruker.com