LabVantage®

ADVANCED INFORMATICS SOLUTIONS FOR DIGITAL DATA MANAGEMENT

Data Integrity in the Pharma Space

The pharmaceutical industry, together with contract research and contract manufacturing organizations (CRO and CMO) must work under Good Manufacturing or Laboratory Practice regulations (GMP or GLP) to ensure the safety and quality of pharmaceutical products. Compliance with these mandatory regulations ensures both data quality and data integrity. Over the past 15 years, there have been many data integrity breaches due either to poor data management practices, reliance on paper or deliberate data falsification.

In the 1970s when the U.S. GLP and GMP were first issued, records were mainly paper-based. Since then, increased computerization has resulted in new regulations and guidance documents that aid interpretation of GMP for the quality and compliance of computerized data systems. Despite this, most of the record-keeping is still paper-based and —even when computerized systems are used — signed printouts can be claimed to be the GMP record.

Other poor data management practices include shared user identities, testing into compliance, failing to backup electronic records, deletion of data, poor time synchronization and use of unnumbered blank forms. Now, regulatory authorities are encouraging pharmaceutical companies to work electronically to ensure data integrity.

Regulatory Compliance – Electronic Records and Computerized Systems

When a computerized system is used for automating regulatory work such as laboratory analysis, there are specific regulations that must be met. The oldest of these is European GMP Annex 11 Computerized Systems which was issued originally in 1992. It was updated in 2011 to enforce data integrity requirements.[1] This regulation outlines ways to validate the system during implementation and provide further control mechanisms. To fully understand Annex 11, it is worth reading Chapter 4 on documentation[2] as it expands on good documentation practices and record retention, which impact computerized systems. Annex 11 can also be supplemented by some of the approaches for computerized systems outlined in EU GMP Annex 15 on qualification and validation.[3]

The U.S. Food and Drug Administration (FDA), has a regulation specific for electronic records and electronic signatures (21 CFR 11).[4] This regulation is applicable to all areas regulated by the agency such as pharmaceutical development, clinical and manufacturing, but it must be interpreted by the applicable predicate (pre-existing) regulation such as 21 CFR 211 for GMP.[5]

Data Integrity and ALCOA+

Although data integrity is implied within the current good practice (GXP) regulations, regulatory authorities have developed the ALCOA+ (ALCOA plus) criteria for data integrity. The ALCOA criteria were originally defined by the FDA, before the European Medicines Agency (EMA)[6] added an additional four criteria resulting in ALCOA+. Together, these nine criteria are important for defining what is meant by the term data integrity and should be applied to both paper and electronic processes to help identify data vulnerabilities.

The nine criteria and the meaning of each are shown in Table 1. These have been reiterated in data integrity guidance documents issued by regulatory authorities such as the Medicines and Healthcare Products Regulatory Agency (MHRA), World Health Organization (WHO), Pharmaceutical Inspection Cooperation Scheme (PIC/S) and FDA[7-10] plus industry bodies Good Automated Manufacturing Practice Forum (GAMP) Parenteral Drug Association (PDA) and Active Pharmaceutical Ingredient Committee (APIC].[11-14]

Table 1: Definition of ALCOA Criteria for Data Integrity

Criterion	Meaning
ATTRIBUTABLE	• The identity of the person or system who executed an action or created, modified or deleted data is captured in the record. • When was the activity performed?
LEGIBLE	• All data are readable, understandable, and allow a clear picture of the sequencing of steps or events in the record so that all GXP activities conducted can be fully reconstructed by the people reviewing these records at any point during the records retention time.
CONTEMPORANEOUS	• Data must be recorded at the time they are generated or observed.
ORIGINAL	• Original record: data in the file or format in which it was originally generated, preserving the integrity (accuracy, completeness, content and meaning) of the record, e.g. original paper record of a manual observation, or electronic data file from a computer-ized system • True or verified copy: an exact verified copy of an original record
ACCURATE	• Data are correct, truthful, valid and reliable with context and meaning. • No editing without documented amendments/audit trail entries by authorized personnel
COMPLETE	• All data from an analysis including any data generated before a problem is observed, data generated after repeating part or all of the work or reanalysis performed on the sample

Criterion	Meaning
CONSISTENT	• All elements of the analysis, such as the sequence of events and follow on data files are date (all processes) and time (when using an electronic system) stamped in the expected order. • A system functions in a repeatable manner.
ENDURING	• Recorded on authorized media, e.g. laboratory notebooks and numbered worksheets for which there is accountability or electronic media proven for the record retention period
AVAILABLE	• The complete collection of records can be accessed or retrieved for review and audit or inspection over the lifetime of the record.

Data Management

These guidance documents imply that the industry should move away from paper, as uncontrolled blank forms[9,10,15] are unacceptable and the administrative burden to continue using and reconciling them is expensive. Therefore, laboratories should automate their processes and eliminate paper records as much as possible.

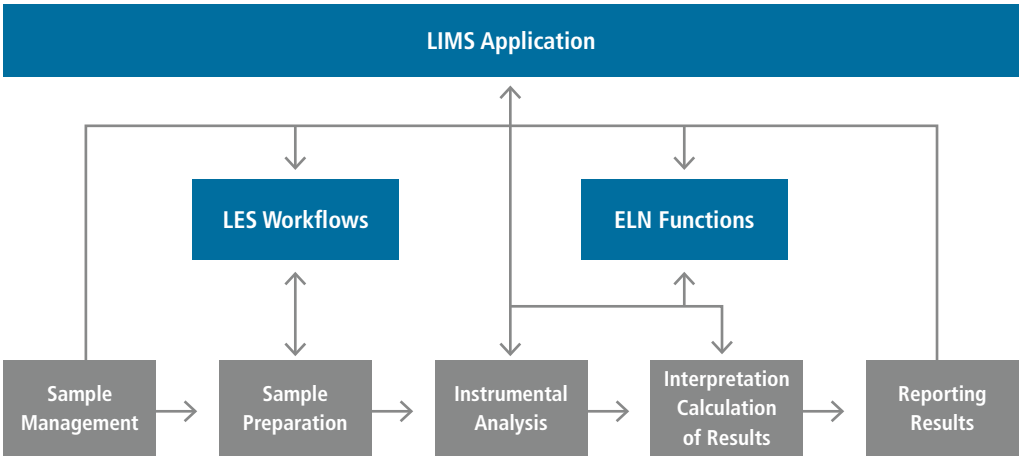
Question 12 of the FDA data integrity guidance[10] asks ***when does a record become a GMP record?*** A critical part of the answer to this question is:

…. it is not acceptable to store electronic records in a manner that allows for manipulation without creating a permanent record.

This is an issue with some analytical instruments where data can be stored in temporary memory until an analyst physically saves or prints the data. This allows multiple attempts at selecting the "right" result before creating a permanent record.

To avoid this situation, we need to consider an advanced informatics solution.

Figure 1: The Analytical Process from Sampling to Reportable Result Automated by an Advanced Informatics Application



Advanced Informatics Solutions

Some of the typical tasks within a regulated laboratory from sample to reportable result are shown in Figure 1 and consist of sampling, sample management, sample preparation, instrumental analysis, data interpretation, calculation of the result and reporting. Of these tasks, the areas automated by traditional Laboratory Information Management Systems (LIMS) are:

- Sample management
- Instrument interfacing
- Result transfer from instrument data systems
- Calculation of results
- Reporting

Sample preparation is typically a manual process which produces paper records that a traditional LIMS does not automate. As such, it is an area where poor record management practices and even falsification can occur as there is little or no evidence of the original data record. To overcome this, Laboratory Execution System (LES) workflows can be integrated into a LIMS to automate a process, eliminate paper and ensure data integrity. For example:

- Within a sample preparation LES workflow, instruments such as pH meters and analytical balances can be integrated so that data can be sent directly to the LIMS database. This means that there is no longer any GMP data held in temporary memory. Additionally, automating the sample preparation workflow eliminates manual data entry by an analyst and transcription error checking by a reviewer.

- Spreadsheets are another area that are a high regulatory risk as they usually consist of electronic records (that should be saved but may not be) linked with signed paper printouts. Using a validated spreadsheet within an Electronic Laboratory Notebook (ELN) environment permits more compliant spreadsheet use. The ELN provides an audit trail to identify who made entries and corrections, data can be imported electronically from an LES workflow if required and paper can be eliminated by electronically signing the completed spreadsheet report.

An example of a modern LIMS platform with integrated LES and ELN functionality is the LabVantage LIMS version 8.4. This LIMS provides the majority of workflows required in a regulated laboratory working in the pharmaceutical and biotechnology industries such as:

- Sample management
- Sample labeling
- Reagent and standard preparation and tracking
- Stability testing
- Instrument calibration and maintenance
- Management by exception
- Incorporation of automatic calculations
- Checks of results against specifications

Note, that this is not an exclusive list of processes and tasks that can be automated by a LIMS/ELN/LES.

LabVantage Pharma is the world's only pre-validated and pre-configured pharmaceutical LIMS which has the benefits of reducing deployment time by 75% and cost by 85% compared to a traditional LIMS implementation.

All these functions within a LIMS/LES/ELN workflow provide regulatory compliance advantages through the technical controls mandated by 21 CFR 11 and EU GMP Annex 11 such as access controls, authority checks, audit trails and checks of data transfers. There is also the business benefit of faster analysis as data is acquired directly and not written down for later manual entry into the LIMS. Furthermore, the major benefit is a faster second person review as there is only the LIMS electronic records to review.

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A recognized leader in enterprise laboratory software solutions, LabVantage Solutions dedicates itself to improving customer outcomes by transforming data into knowledge. The LabVantage informatics platform is highly configurable, integrated across a common architecture, and 100% browser-based to support hundreds of concurrent users. Deployed on-premise, via the cloud, or SaaS, it seamlessly interfaces with instruments and other enterprise systems – enabling true digital transformation. The platform consists of the most modern laboratory information management system (LIMS) available, integrated electronic laboratory notebook (ELN), laboratory execution system (LES), and scientific data management system (SDMS); and, for healthcare settings, a laboratory information system (LIS). We support more than 1500 global customer sites in the life sciences, pharmaceutical, medical device, biobank, food & beverage, consumer packaged goods, oil & gas, genetics/diagnostics, and healthcare industries. Headquartered in Somerset, NJ., with global offices, LabVantage has, for four decades, offered its comprehensive portfolio of products and services to enable customers to innovate faster in the R&D cycle, improve manufactured product quality, achieve accurate record-keeping, and comply with regulatory requirements.

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