WHITE PAPER

Thermo Fisher Informatics Solutions

Enabling data integrity from drug discovery through manufacturing

Promoting an environment to ensure high quality data

When discussing the success of a drug therapy, a common topic amongst biopharmaceutical companies is data quality and data integrity; what the challenges are and what the key elements are to ensuring that the latest discovery is patentable, does not result in re-conducting critical research or development studies, is accepted by the regulators, or does not result in a recall of a batch of product. A common challenge expressed amongst the industry is how to implement processes that promote and ensure that regulatory guidance's are being followed and that their data is of the highest integrity. High data quality and integrity is critical to ensure patient safety and drug efficacy from research and development through to manufacturing.

How good documentation practices enable data integrity within a research setting

Although research laboratories do not need to adhere to comprehensive regulatory guidances mandated by organizations such as the FDA, EMA, PMDA, and MHRA, it is critical that they follow Good Documentation Practice (GDP) to ensure data integrity. As stated by the NIH, "Good science requires good record keeping. Good record keeping promotes both accountability and integrity in research."[1]. Good Documentation Practices uphold the quality of data and provide assurances to research leaders, patent reviewers, and regulatory agencies that studies were conducted carefully, thoughtfully, and of high scientific integrity. Following the documentation practices of ALCOA, ensures that data is Attributable, Legible, Contemporaneous, Original and Accurate, providing confidence in the results that are reported.

Inadequate records can cause difficult project hand-offs between research teams, delayed patent filing process, and, in severe cases, rejection of data by regulators in an Investigational New Drug (IND), Biologics Licensing Application (BLA), and New Drug Application (NDA). In drug discovery, the transfer of knowledge of data generated and conclusions formed from target identification, to upstream processing, and high-throughput screening teams is critical for research leaders to make a go-no-go decision on future investments into pre-clinical studies. All data must be reviewed to ensure its validity before it moves to the next phase in the drug discovery process. When data is not properly recorded, it also impacts patent filing. If a patent application is challenged, research teams have to spend large amounts of time looking for data that may have been documented in a lab notebook and/or spending time and resources re-discussing or reconducting studies to provide essential data for a patent.

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For example, when filing a BLA with a regulatory body, an issue that has arisen for Sponsors, is that the original discoverers did not track their work well enough, i.e. not tracking what methods were used, what gender of animals were used or what the lot information was for the drug product used in preclinical studies. This can result in regulatory agencies rejecting pieces of a submission and asking the Sponsor to re-conduct studies, or more seriously a Refuse-to-File (RTF) as outlined in the guidance to industry "Refuse to File: NDA and BLA Submissions to CDER,", causing a significant impact to the timeline and budget of a project.

Section 21CFR601.2(a) states "An application for a biologics license shall not be considered as filed until all pertinent information and data have been received by the Food and Drug Administration"[2].

Data quality and data integrity is vital and incredibly valuable to the success of a therapeutic program Laboratory Information Management Systems (LIMS) and Electronic Laboratory Notebooks (ELN), provide research organizations with a mechanism to ensure that their scientific data is captured, documented, stored, witnessed, and archived in a safe and secure manor.

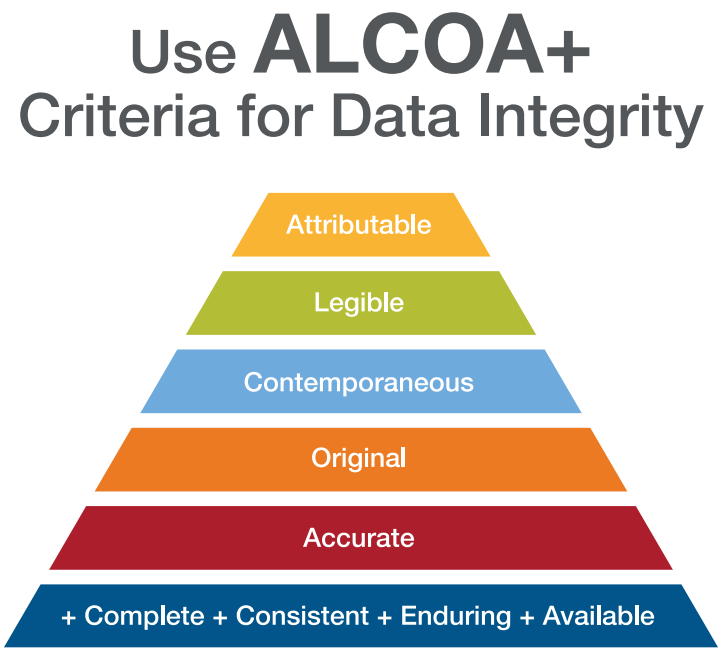

fig.1. The principles of ALCOA ensure that data is recorded completely, consistently, and available for future reference and use.

Producing data of high quality and integrity throughout bioanalytical studies

Laboratory analysis is just one component in controlling and ensuring data integrity during a bioanalytical study. Data integrity in a bioanalytical laboratory goes beyond non-clinical and clinical data capture, it stems into many other processes such as sample and analyte shipping and stability, study and sample management, method and instrument validation, training, and documentation. The data produced by bioanalytical laboratories is vital in supporting BLA and NDA submissions, as well as phase 1-4 clinical trials. The challenge for bioanalytical laboratories is ensuring that they are complying with the latest regulatory documents set forth by regulatory agencies in each of the countries where they plan to file in.

Bioanalytical laboratories are required to comply with regulatory guidance documents such as, Guidelines for Bioanalytical Method Validation (EMA and FDA), 21CFR58, and 21CFR11, from method development through study archival. Procedural elements for data integrity in a bioanalytical laboratory can be broken down into three elements integrity of the analyte and data produced, integrity of the sample identity, and integrity of documentation[3]. Integrity of the analyte or drug product needs to be maintained from manufacturing of the drug product, to handling, shipment, and storage procedures. This includes ensuring that the product certificate of analysis is attached to each analytical run and that the same lot of drug product is used from method development throughout sample analysis, providing consistency in results.

Without complete knowledge of the conditions that an analyte has been through, the accuracy of assay data will be called into question by an inspector. It is crucial to have full chain of custody for any movement that is made to the analyte, for example, temperature monitoring records must be included with shipping records, and all movements into and out of storage must be tracked and monitored. Failure to accurately track these methods can jeopardize the credibility of the bioanalytical study as incorrect procedures can affect the stability or change the composition of an analyte.

Ensuring integrity in the sample identity and sample data encompasses many different bioanalytical processes such as instrument validation, method validation, sample management, and laboratory analysis. Validation of computerized systems and laboratory equipment is a key factor in ensuring the accuracy and reliability of data that is generated or produced from those systems. Laboratories must conduct validation of systems according to 21 CFR Part 11, this provides assurance that the system is consistently producing expected results and complies with security requirements, enabling high data integrity. The Guideline for Bioanalytical Method Validation explicitly details all analytical methods that must be conducted for assays used in clinical analysis. The rigor of the method validation guidance, provides credibility and integrity in the data that is generated from clinical assays. If a method fails to comply with the bioanalytical guidance then the results produced in clinical analysis cannot be fully trusted by auditors due to a lack of confidence in the performance of the assay.

It is vital that a Principal Investigator in a bioanalytical study can walk an auditor through the complete life cycle or chain of custody of a non-clinical or clinical sample. This allows the auditor to review your sample accessioning process which must comply with Good Laboratory Practices (GLPS) and Good Clinical Practices (GCPs). Auditors must be able to see documentation related to how the sample was received and stored, documentation of any discrepancies in the shipment or sample manifest, and each freeze/thaw of the sample, including movement for analytical runs (i.e time at benchtop and temporary refrigerator storage). Without a complete chain of custody, the credibility of the sample and therefore the analytical results can be called into question. Laboratory analysis plays a crucial role in data integrity.

Each step of an analytical Standard Operating Procedure (SOP) must be strictly followed according to the method validation, and must have each step of the assay documented including instruments, materials, and reagents used. Adherence to each step of the analytical SOP ensures the integrity of laboratory results can be trusted as of high integrity because it ensures the analyte and sample management procedures have been executed using a validated instrument and method. This leads to another crucial piece of ensuring data integrity, integrity of documentation. Each process in a bioanalytical laboratory that comprises a bioanalytical study must be fully documented, including training records on all SOPs for instrument use, reagent creation, analytical methods, and data analysis. Study and assay documentation must follow the principles of ALCOA. Principal Investigators must be able to show an auditor that those conducting the study are trained and fully competent for their role in the study. Sponsors must be able to fully recreate each step of a bioanalytical study for an auditor.

Ensuring compliance with many regulations can be a challenging task for the bioanalytical community. Thermo Scientific™ Watson LIMS™ software enables bioanalytical laboratories to comply with guidance documents and to ensure integrity in their data. Watson LIMS software provides complete traceability from study initiation through study closeout. It provides Principal Investigators with a quick mechanism to provide an auditor with a sample's chain of custody, an assay's method validation, source analytical run data, study reports, ISR results, or the justification for repeat analyses. Watson LIMS software provides Principal Investigators with a 360° view of their bioanalytical study, offering confidence and enabling compliance in their study.

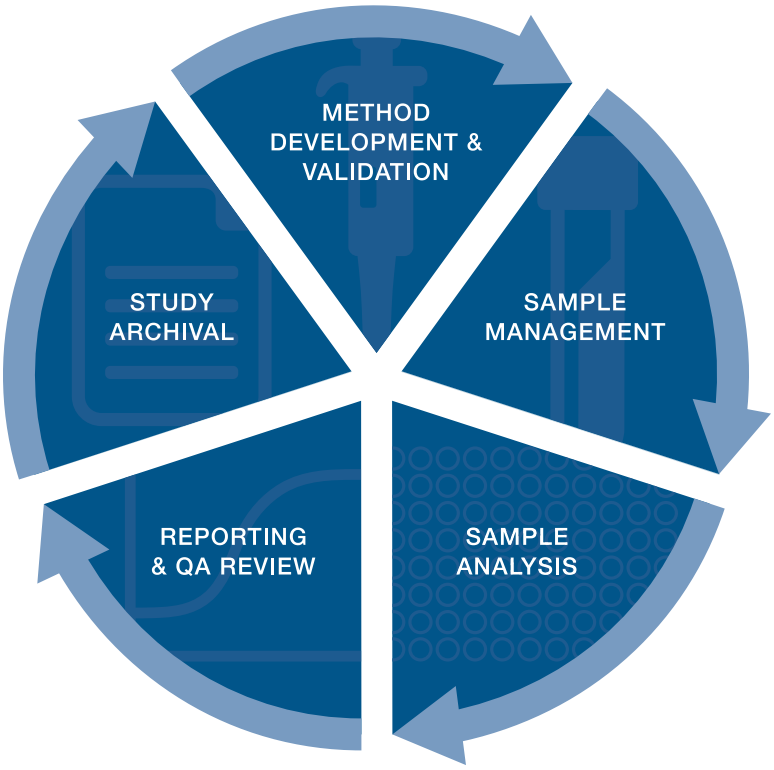

fig.2. Bioanalytical studies require that they can be completely recreated by an auditor, each phase of a bioanalytical study must be documented to ensure complete visibility.

Ensuring high quality results during product manufacturing

Similar to the necessity to adhere to GLPs during toxicology and pharmacology studies, biopharmaceutical companies and contract manufacturing organizations (CMOs) must comply with Current Good Manufacturing Practices (CGMPs) when manufacturing a drug product. Section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351 (a)(2)(B)) requires drugs, which include IND products, to comply with current good manufacturing practice as follows: "A drug...shall be deemed adulterated...if...the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess."[4] Many different controls need to be in place to ensure that the mandates set forth by regulatory agencies such as the FDA are followed.

Quality systems must be implemented before the manufacturing of a drug product takes place and provides an overarching umbrella to manufacturing processes. A quality system must be implemented to surround the various manufacturing systems: production system, facilities and equipment system, laboratory controls system, materials system, packaging and labelling system, and production system[5]. Establishing quality systems according to the FDA's guidance for industry, Quality Systems Approach to Pharmaceutical CGMP Regulations, ensures data integrity in the drug products manufactured, and ultimately assurances to auditors and consumers of the drug product.

Beginning with process validation, manufacturers must comply with CGMPs. Process validation is defined as the collection and evaluation of data, from the process design stage through commercial production. This establishes scientific evidence that a process is capable of consistently delivering a product, and therefore, ensuring high data integrity. Process validation can be broken down into 3 stages, process design, process qualification, and continued process verification.

Process design encompasses development and scale-up activities, it is critical that these teams accurately detail all methods used and data reported, again following the principles of ALCOA, to enable a fluid and complete hand-off for manufacturing. Implementation of an effective process with effective process controls is dependent on the knowledge gained from process development. Furthermore, results from the Design of Experiment (DOE) can assist in providing justification for establishing attributes such as ranges of incoming component quality, equipment parameters, and in-process material quality attributes[6]. Aligning manufacturing methods with process development methods assures that data is accurate and consistent. Critical to providing a quality product is implementing Quality by Design (QbD), the elements of a QbD program as stated in The AAPS Journal article, Understanding Pharmaceutical Quality by Design include:

- A Quality target product profile (QTPP) that identifies the critical quality attributes (CQAs) of the drug product
- Product design and understanding including the identification of critical material attributes (CMAs)
- Process design and understanding including the identification of critical process parameters (CPPs) and a thorough understanding of scale-up principles, linking CMAs and CPPs to CQAs
- A control strategy that includes specifications for the drug substance(s), excipient(s), and drug product as well as controls for each step of the manufacturing process
- Process capability and continual improvement

Data generated from QbD experiments helps scientists to understand both the product and the process, these parameters come together to ensure a quality product[7].

During process qualification, equipment and utilities are qualified and validated and process performance qualification (PPQ) is executed. Protocol execution plans and results must be fully documented to show what was planned to be qualified (with expected results) and then what the final reported results were. Successful PPQ confirms that the process design is capable of producing the commercial product as expected. The execution of equipment, instrument, and process qualification provides auditors with the assurance that the data that is generated is of high integrity and can be trusted for commercial manufacturing. Over time, it is required that manufacturers perform continued process verification. Data that is collected in phase must include relevant process trends and quality of incoming materials, in-process material, and finished product. The data that is produced from ongoing evaluations must be analyzed by a trained statistician to ensure accuracy in data results.

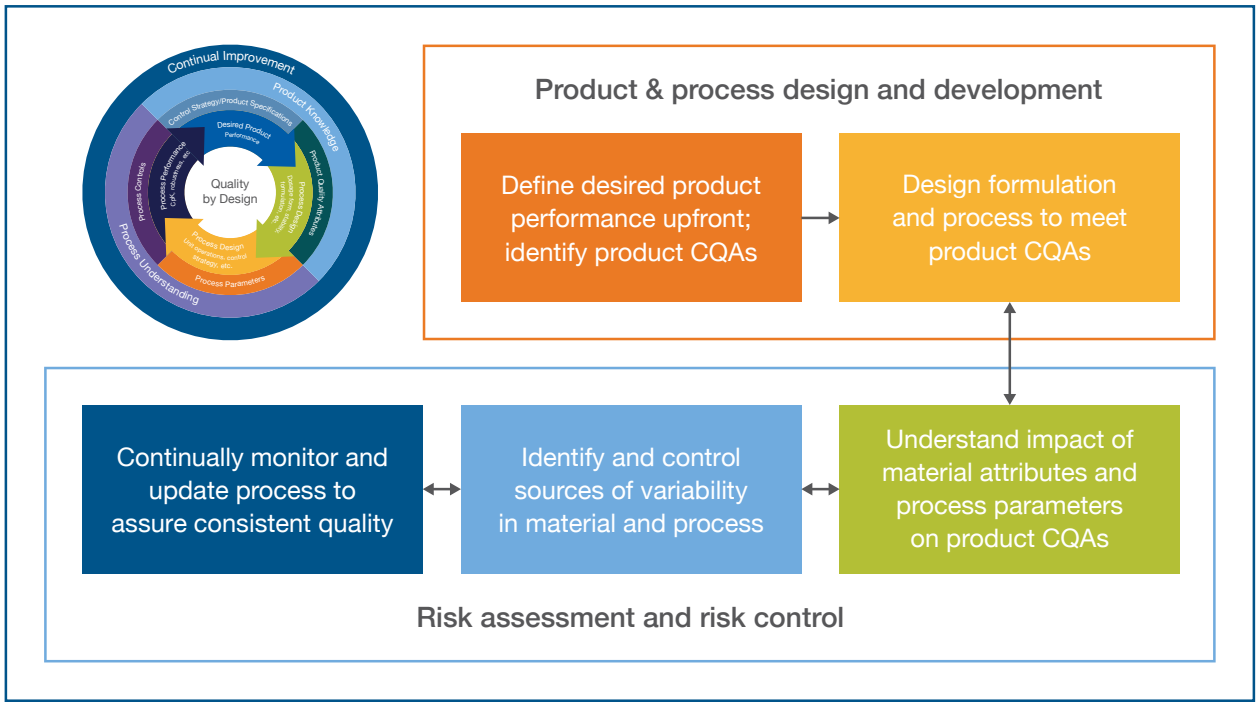

fig.3. FDA requires that processes are put in place to ensure high quality in drug products.

Documentation is critical throughout each step of the manufacturing process from process design through commercial manufacturing. Complete documentation of each step in the process provides legitimacy in the data that is produced, and allows auditors to continue to allow production of the drug product. Failure to comply with the regulations set forth by regulatory agencies can result in the issuance of an observation letter such as a 483 by the FDA. Thermo Scientific™ SampleManager LIMS™ software drives productivity, enables compliance, streamlines manufacturing processes, and improves organization efficiency. SampleManager LIMS software delivers laboratory management, data management, and process execution/procedural ELN (LES) capabilities in one system. The ability to capture and document all relevant manufacturing product data in one system, eases an audit situation and ultimately provides the highest level of integrity to data.

Providing safety to patients with data integrity

Producing data that is of high scientific integrity is an onerous and rigorous process. However, implementation and adherence to regulatory guidance documents and regulations from research and development through manufacturing ensures that patients, are being given treatments that are safe and effective. Utilization of software systems such as Watson LIMS, and SampleManager LIMS software enables and promotes compliance with regulations at each phase of the discovery, development, and manufacturing of a drug.

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