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GLP Bioanalysis from the US FDA Perspective

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The United States Food and Drug Administration is responsible for ensuring US residents receive safe and effective medicines. Since blood levels of drugs are correlated with pharmacological effect, FDA closely regulates how those blood levels are measured. The FDA has established requirements for bioanalytical analyses such as minimum method validation, SOP, and reporting criteria. The FDA also has standards for computer validation which must be followed to ensure the data are reliable. Data presented to the Agency are scrutinized to ensure they are accurate and a true reflection of the raw data generated in a study. To verify the quality of data, FDA has developed an inspection program. The specific requirements of the FDA related to bioanalysis will be discussed.



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Introduction

The US FDA closely regulates bioanalysis

- Good Laboratory Practices (GLPs)
- Bioanalytical Method Validation Guidance
- Bioresearch Research Monitoring Guide



GLPs

Require the Study Director to be informed of all issues which could affect the quality and integrity of the study

Require an independent QA Unit to conduct inspections of critical phases of a study at sufficient intervals to guarantee the quality of the results



Bioanalytical Method Validation Guidance

Establishes *minimum* standards for bioanalytical validations

Requires evaluation of precision, accuracy, selectivity, sensitivity, reproducibility, and stability

Requires a method to be accurate and precise and suitable for its intended use



Guidance (continued)

Requires SOPs covering all aspects of bioanalysis from sample receipt to reporting results

Lists requirements for reporting validation results

Bioresearch Monitoring Program

Establishes guidelines for the conduct of FDA inspections
Mainly related to the animal portion of studies but does cover the bioanalytical portion
Describes the procedure for reporting inspection results

Standard Operating Procedures (SOPs)

Should cover all operational aspects of the bioanalytical laboratory

- General laboratory organization and function
- Training
- Method Validation

Standard Operating Procedures (SOPs)

- Sample Analysis
- Quality Control Processes
- Reporting of Data
- Laboratory Instrumentation

Documentation

Must be complete and allow reconstruction of the entire study
If an SOP requires something to be done, it must be documented
In the FDA's view, if it is not documented, it did not happen
Original documentation is "Raw Data"

Computer Systems

If a computer system

- Records raw data (e.g. chromatograms)
- Performs calculations on raw data
- Reports raw data

Then the computer system must be validated

Computer Systems (continued)

A computer system is defined as the software and the environment in which it operates.
This means software must be validated on the same platform and under the same conditions as it will be used.
The extent of validation required is directly related to the importance of the system.

FDA Inspections

Surveillance Inspections are periodic, routine determinations of a laboratory's compliance with GLP regulations. These inspections include a facility inspection and audits of on-going and/or recently completed studies.

FDA Inspections (continued)

Directed Inspections are assigned to achieve a specific purpose, such as:

- Verifying the reliability, integrity, and compliance of critical safety studies being reviewed in support of pending applications.

FDA Inspections (continued)

- Investigating issues involving potentially unreliable safety data and/or violative conditions brought to FDA's attention.

FDA Inspections (continued)

- Re-inspecting laboratories previously classified OAI (usually within 6 months after the firm responds to a Warning Letter).
- Verifying the results from third party audits or sponsor audits submitted to FDA for consideration in determining whether to accept or reject questionable or suspect studies.

FDA Inspections (continued)

FDA will examine:

- Facilities
- SOPs
- Personnel
 - Training
 - Experience
 - Workload

FDA Inspections (continued)

All study data and documentation

FDA will confirm the data reported was an accurate and complete representation of the study and it was generated in compliance with all applicable regulations, SOPs and industry standards.

Conclusion

For US FDA acceptance of bioanalytical analyses the following criteria must be met:

- SOPs must cover all areas of bioanalysis
- Documentation must be clear and complete
- Computer systems must be validated
- Facilities must be adequate for the workload

Conclusion

- Staff must be qualified by experience or training
- There must be a sufficient number of staff for the workload
- Data reported to the FDA must be a true and accurate reflection of the raw data.