Data Integrity for In Vivo Bioavailability and Bioequivalence Studies

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

April 2024
Generic Drugs

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Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to provide recommendations to applicants and testing site[2] management[3] on achieving and maintaining data integrity for the clinical and bioanalytical portions of bioavailability (BA) and bioequivalence (BE) studies submitted in support of investigational new drug applications (INDs), new drug applications (NDAs), and abbreviated new drug applications (ANDAs), and the bioanalytical portion of clinical pharmacologic studies supporting CDER-regulated biologic license applications (BLAs) as well as amendments and supplements to these applications.[4,5,6] In addition, the recommendations in this guidance apply to the bioanalytical portion of nonclinical studies. FDA also encourages applicants and testing sites to consider these recommendations when conducting other studies, including in vitro and pharmacology and toxicology studies.

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[1] This guidance has been prepared by the Office of Generic Drugs (OGD), and the Office of Study Integrity and Surveillance (OSIS) and the Office of Clinical Pharmacology (OCP) in the Office of Translational Sciences (OTS) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] This guidance uses the term "testing sites" when referring to sites that conduct the clinical portion of the study, the bioanalytical portion of the study, or both; the term "clinical testing sites" when referring to sites that only conduct the clinical portion of the study; and the term "analytical testing sites" when referring to sites that only conduct the bioanalytical portion of the study.

[3] As stated in section III.B of this guidance, testing site management is responsible for the organization and functioning of the sites where BA and BE studies are conducted or analyzed. The role(s) included in testing site management for a particular site could vary depending on whether it is a clinical testing site, analytical testing site, or both.

[4] The term "applicant" as used in this guidance refers to both sponsors of INDs and applicants of NDAs, ANDAs, and BLAs.

[5] When discussing the recommendations for achieving and maintaining data integrity, this guidance will generally reference BA and BE studies. As stated, the recommendations also apply to clinical pharmacologic studies supporting CDER-regulated BLAs.

[6] In addition to the recommendations in this guidance, clinical testing sites should conduct the clinical portion of the study using good clinical practice to ensure participant safety and data integrity.

FDA expects that all data submitted to the Agency are accurate, complete, and reliable, and that applicants and testing sites achieve and maintain data integrity throughout the data lifecycle of the product(s) or biologic therapeutic(s) (see section II – Background). This guidance provides recommendations to achieve and maintain data integrity with respect to (1) applicants, (2) testing site management, and (3) implementation and management of a quality management system.

This guidance does not include a comprehensive list of all best practices that applicants and testing site management should use to achieve and maintain data integrity. It is each applicant's responsibility to achieve and maintain data integrity for their studies, which includes identifying and implementing the most effective and efficient risk-based controls. FDA encourages applicants and testing site management to review FDA regulations and all applicable guidance for industry to understand FDA's current thinking on a topic.[7]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

Requirements for submitting BA and BE data in INDs, NDAs, ANDAs, and amendments and supplements to these applications, the definitions of BA and BE, and the types of in vitro and in vivo studies that are appropriate to measure BA and establish BE are set forth in 21 CFR parts 312, 314, and 320. Requirements for BLAs and amendments and supplements to these applications are included in 21 CFR part 601. FDA expects that all data submitted to the Agency, including data from BA and BE studies submitted in support of INDs, NDAs, and ANDAs and clinical pharmacologic studies submitted in support of BLAs, is accurate, complete, and reliable, and that industry maintain data integrity throughout the data lifecycle of the product(s) or biologic therapeutic(s).

For purposes of this guidance, *data integrity* refers to the accuracy, completeness, and reliability of data. Accurate, complete, and reliable data should be attributable to the person generating the data, legible, contemporaneously recorded, original or a true copy, and accurate (ALCOA).[8] These characteristics of the data should be maintained throughout the data lifecycle.

[7] This guidance includes references to other FDA guidances that address topics related to data integrity. For example, see the guidance for industry *Data Integrity and Compliance with Drug CGMP – Questions and Answers* (December 2018). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[8] See the guidance for industry *Data Integrity and Compliance with Drug CGMP – Questions and Answers* (December 2018) which also discusses ALCOA. See also the OECD Advisory Document of the Working Party on Good Laboratory Practice on GLP Data Integrity (September 2021), available at https://one.oecd.org/document/env/cbc/mono(2021)26/en/pdf.

Data integrity is different from *data quality*. For purposes of this guidance, *data quality* refers to the assurance that data produced are generated in compliance with applicable standards and can be used for its intended purpose.[9] Data quality impacts whether data is fit for purpose and whether data is acceptable for regulatory decision-making.

In recent years, FDA has observed data integrity concerns during the inspection of testing sites, clinical testing sites, and analytical testing sites, and during the assessment of the BA and BE study data submitted in support of applications. Data integrity concerns can impact application acceptance for filing, assessment, regulatory actions, and approval as well as post-approval actions, such as therapeutic equivalence ratings.

Achieving and maintaining data integrity is an important component of industry's responsibilities to ensure the safety, efficacy, and quality of drug products and biological therapeutics. It is the role of industry, specifically management with executive responsibility, to create a quality culture where personnel understand that data integrity is an organizational core value and personnel are encouraged to identify and promptly report data integrity issues.[10] In the absence of management support of a quality culture, systems can break down and lead to errors and misconduct.

The recommendations in this guidance are for applicants as well as testing site management. Additionally, this guidance includes recommended elements for implementing a quality management system. For purposes of this guidance, *quality management system* refers to the organizational structure, responsibilities, procedures, and resources for achieving and maintaining data integrity throughout the data lifecycle.

The recommendations in this guidance are primarily focused on electronic data, but these recommendations can also be applied to other data types and formats.

FDA strongly encourages individuals, testing sites, and applicants who identify potential evidence of fraud, manipulation, or mismanagement in the conduct of BA or BE studies to report such concerns to FDA at DrugInfo@fda.hhs.gov. This additional reporting method is not intended to supersede and does not replace other FDA reporting requirements (e.g., field alert reports).

[9] See also the OECD Advisory Document of the Working Party on Good Laboratory Practice on GLP Data Integrity (September 2021), available at https://one.oecd.org/document/env/cbc/mono(2021)26/en/pdf.

[10] See the guidance for industry *Data Integrity and Compliance with Drug CGMP – Questions and Answers* (December 2018).

III. DISCUSSION

A. Recommendations for Applicants

The complexity of drug products and BA and BE studies as well as the number of firms involved in conducting these studies have expanded in recent years. Applicants can conduct BA and BE studies themselves or contract with testing sites to conduct all or parts of the BA and BE studies, such as the clinical portion, the analytical portion, or general study-related activities (e.g., packaging or preparing the study drug for dosing, or electronic systems development or use throughout a study). Although applicants can contract with testing sites, the ultimate responsibility for the quality and integrity of the BA and BE study data resides with applicants.[11]

Applicants should ensure the integrity and confidentiality of data generated by and managed for BA and BE studies and applicants should implement an appropriate system to manage data quality throughout all stages of the BA and BE study.[12] The applicant's quality management system should include the design and implementation of efficient protocols including tools and procedures for study conduct (including data collection and management) to support participant's rights, safety, and well-being and the reliability of study results.[13]

When applicants conduct all or parts of the BA and BE studies themselves, the applicants should review applicable FDA guidances and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines and perform the studies in compliance with all applicable statutes and FDA regulations. Applicants should also consider the recommendations in this section as well as the recommendations provided under the Recommendations for Testing Site Management (section III.B).

When applicants contract with testing sites to conduct all or parts of the BA and BE studies, such as the clinical portion, the analytical portion, or general study-related activities, applicants should ensure that the testing sites review applicable FDA guidances and ICH guidelines and perform all contracted study-related activities in compliance with all applicable statutes and FDA regulations. Applicants should also consider requiring that the testing sites implement and manage a quality management system (see section III.C– Elements of a Quality Management System of this guidance) to ensure integrity of the data submitted to FDA in support of their applications.

[11] See the draft guidance for industry *E6(R3) Good Clinical Practice* (June 2023). When finalized, this guidance will represent the FDA's current thinking on this topic.

[12] Ibid.

[13] See the draft guidance for industry *E6(R3) Good Clinical Practice* (June 2023) for more information. When finalized, this guidance will represent the FDA's current thinking on this topic. See also the guidance for industry *E8 (R1) General Considerations for Clinical Studies* (April 2022).

Recommendations for applicants include:

1. Testing Site Selection

Applicants should use qualified testing sites, taking into consideration the education, training, and experience of the testing site's personnel, the testing site's quality management system (see section III.C – Elements of a Quality Management System of this guidance), and the testing site's history of inspectional findings by FDA and foreign regulators to perform the contracted study-related activities.

Applicants should provide testing sites with the information necessary to conduct the contracted study-related activities. Testing sites should agree in writing that they understand and will implement the applicable regulatory requirements for the contracted study-related activities, as well as the study protocol, procedures, and processes.

Testing sites should be adequately resourced in terms of the equipment, personnel, computerized systems, etc., to perform the contracted study-related activities. The reporting structure of the testing site should be open and transparent for personnel at all levels to freely communicate errors and failures that impact data integrity.

2. Monitoring and Oversight

a. Monitoring Plan

Applicants should develop and use a monitoring plan to ensure that testing sites are appropriately assessing, controlling, communicating, and reviewing risks[14] to the quality and integrity of study data and protecting participants enrolled in the study. The procedures and processes tailored to monitor the critical aspects of the studies should be clearly delineated from and be independent of the testing site's quality assurance monitoring plans. As part of the monitoring plan, applicants should conduct audits to verify testing sites' compliance with the monitoring plan (see section III.A.2.b of this guidance).

Applicants should understand and consider the entire data-flow in developing and using their monitoring plan. For example, data files created on local systems to export data to network area folders after acquisition and processing should not be modified without an audit trail. Monitoring computerized interfaces for moving or transforming data between different validated instruments and software systems is critical to ensuring data integrity.[15]

[14] Risks to data include, but are not limited to, the potential to be deleted, amended, or excluded without authorization or without detection. See the guidance for industry *Data Integrity and Compliance with Drug CGMP – Questions and Answers* (December 2018).

[15] For additional information on computerized systems, see the guidance for industry *Computerized Systems Used in Clinical Investigations* (May 2007). See also the draft guidance for industry *Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations* (March 2023). When final, this guidance will supersede the guidance for industry *Computerized Systems Used In Clinical Investigations* (May 2007) and will represent the FDA's current thinking on this topic.

Applicants should assess data integrity risks at the systems level (e.g., adequacy of standard operating procedures (SOPs), computerized systems, training of personnel) and operational level (e.g., design, complexity, size, duration of studies, adequacy of participant screening, informed consent process, data collection).

The extent of monitoring should be proportionate to the risk that the data may be compromised. For example, the bioanalysis of participant samples from in vivo BA and BE studies is essential to those studies providing pivotal data in support of approval of the drug product application. FDA has increasingly found that the inability to verify and rely on the bioanalysis of participant samples from those studies undermines the reliability of the clinical study data, jeopardizing application approvability and making the risks that study participants were exposed to by participating in the studies unjustifiable. Therefore, bioanalytical portions of the studies may warrant closer oversight and monitoring by applicants to ensure that the performance of the analytical methods used for in vivo BA and BE studies are in accordance with the applicable FDA regulations and recommendations, based on its intended purpose.

Steps where there is human intervention in how and what data are recorded, reported, or retained may pose greater risk to data integrity than automated steps and therefore may warrant closer monitoring by applicants.

b. Audits

FDA recommends that applicants conduct audits to verify testing sites' compliance with the monitoring plan. Audits are effective, for example, when performed by trained personnel knowledgeable in principles of clinical investigations, including protection of the rights, safety, and welfare of study participants, data monitoring, statistical monitoring, and study-specific requirements. The auditor conducting the audit should understand the criticality and risk/liabilities of the data governance structure of a testing site.

Audits should verify, including but not limited to, the following:

- The testing site and investigators are complying with the contracted responsibilities.
- Critical study-related activities are performed in accordance with the protocol requirements and applicable statutes and regulations.
- The testing site maintains data integrity (including all manual and automated systems and processes critical to data integrity) throughout the data lifecycle.
- Discrepancies, if any, between data and *metadata* (defined in section III.C.2.b) are investigated.

Audit findings should not influence the outcome of the study or give provisions to amend data generated by the testing sites.

c. Documenting and Communicating Audit Findings

The applicant's audit should be documented with sufficient detail, including dates and monitoring activities, to allow verification that the monitoring plan was followed. If the applicant uses a third-party to conduct the audit, the applicant should review the audit report. The description of any noncompliance, data irregularities, or other deficiencies identified as part of the audit should be communicated to appropriate testing site management and study personnel[16] in a timely manner for review and follow up. All deviations from the monitoring plan and remediation efforts should be recorded.

All communication between applicants and testing sites, as well as any third parties involved in the audit, if any, should be documented to allow verification of study decisions and input from applicants. These communications should be maintained by the applicant as well as at the testing site.

B. Recommendations for Testing Site Management

Testing site management is responsible for the organization and functioning of the sites where BA and BE studies are conducted or analyzed. FDA recommends that testing site management with executive responsibility[17] consider taking the following actions:

- Establish and maintain adequate organizational structure to ensure that BA and BE studies are conducted and analyzed in accordance with the applicable statutes and regulations.

- Ensure that there are qualified, trained personnel and adequate resources, including facilities, equipment, and materials available to ensure that the BA and BE studies are conducted and analyzed in accordance with applicable statutes and regulations.

- Establish the appropriate responsibility, authority, and interrelation of all personnel who manage, perform, and assess work affecting data for BA and BE studies and communicate personnel's roles, responsibilities, and authorities within the organization, ensuring that interactions are defined and understood.[18]

- Establish policies and objectives for data integrity and ensure that these policies and objectives are understood, implemented, and maintained at all levels of the organization.

- Create and encourage a quality culture (discussed in more detail below).

[16] This could include, for example, the study director, the principal investigator, and/or the study investigator.

[17] For purposes of this guidance, *testing site management with executive responsibility* means those senior employees who have the authority to establish or make changes to the testing site's data integrity policies and procedures.

[18] See the guidance for industry *Quality Systems Approach to Pharmaceutical CGMP Regulations* (September 2006).

- Implement and maintain a quality management system (discussed in more detail below).

A quality culture and a quality management system when used together along with the other recommendations for testing site management included above, can assist with achieving and maintaining data integrity for BA and BE studies. A quality culture is about an environment where personnel understand how their actions impact data integrity whereas a quality management system is all of the measures (e.g., training, communication) used to help ensure data integrity.

In a quality culture, personnel understand that data integrity is an organizational core value, personnel are encouraged to identify and promptly report data integrity issues, and management demonstrates a commitment to quality and promotes employee engagement and empowerment.[19]

The following are examples of actions that testing site management can take to help create and encourage a quality culture:

- Set the expectation that data quality and data integrity are the responsibility of everyone in the organization.
- Communicate management's expectations on data integrity to personnel at all levels of the organization in a manner that encourages personnel to report failures, data integrity issues, and opportunities for improvement.
- Provide data integrity training to all personnel who interact with BA and BE study data and perform study activities.
- Encourage open and transparent communication between all levels of the organization, especially for reporting data integrity concerns.
- Create shared accountability for ensuring data integrity.
- Act proactively rather than reactively to prevent data integrity concerns from arising.
- Implement meaningful process and system improvements and make process and system improvements routine practice in the organization's culture.

A quality culture can enable a testing site to prevent data integrity concerns from arising or to identify potential risks and detect data integrity issues earlier than if the testing site did not have a quality culture. In the absence of a quality culture or management support of a quality system, measures put in place at the testing site to ensure data integrity (such as a quality management

[19] See the guidance for industry *Data Integrity and Compliance with Drug CGMP – Questions and Answers* (December 2018).

system) can break down and a testing site may fail to take sufficient action to identify potential risks and prevent and address data integrity issues.

In addition to creating and encouraging a quality culture, FDA recommends that testing site management implement and maintain a quality management system (discussed in more detail in section III.C – Elements of a Quality Management System).

With a robust quality management system, testing site management should demonstrate strong and visible support for the system and ensure its implementation throughout the organization, which also goes toward encouraging a quality culture. For example, testing site management should periodically assess the effectiveness of systems, policies, and procedures. Testing site management should also establish procedures for identifying training needs, ensuring that personnel are adequately trained to perform the assigned tasks, and assessing personnel's understanding about the importance of data integrity.

C. Elements of a Quality Management System

FDA recommends that testing sites where BA and BE studies are conducted or analyzed implement and use a quality management system to help ensure data integrity. Applicants should expect that testing sites implement and manage a quality management system and should take this into consideration in selecting a testing site.

This section discusses elements that should be included in a quality management system. This section does not include an exhaustive list, and other elements may apply. Testing sites should identify and implement the most effective and efficient risk-based controls based on their processes and procedures and applicants should take this into consideration in selecting a testing site.

The testing site should maintain the relevant documents describing the quality management system.

Testing site management's review of the quality management system is key to ensuring its continuing suitability, adequacy, and effectiveness.[20] Testing site management should periodically review the quality management system for effectiveness according to a planned schedule and update or revise it, as necessary. When developing and implementing a new quality management system, reviews should take place more frequently than when the quality management system has matured.[21]

Documentation described in this section should be made available for FDA inspection.

[20] See the guidance for industry *Quality Systems Approach to Pharmaceutical CGMP Regulations* (September 2006).

[21] Ibid.

1. Data Governance and Data Lifecycle

The quality management system should include data governance throughout the data lifecycle.

Data governance is the sum of total arrangements to ensure data integrity (i.e., that data are complete, consistent, accurate, trustworthy, and reliable). Data governance should address the roles, responsibilities, and accountability throughout the data lifecycle of the product or biologic therapeutic.

Data lifecycle includes all phases in the collection of the data, including generation, recording, modification, processing, maintenance, storage, retrieval, transmission, and disposition.

Testing sites can consider using a risk management approach to determine the importance of each data lifecycle phase.

2. Records Management

Data should be retained in such a manner that they are protected, enduring, readily retrievable and remain readable through the records retention period and in compliance with applicable requirements. This includes collection and documentation, analysis, storage, backup, retrieval, and archival.

Testing sites should consider segregating duties between data lifecycle phases, which may reduce the opportunity for personnel to intentionally manipulate data.

a. Computer or Related Systems

Computer or related systems can be used to create, record, modify, process, maintain, store, secure, retrieve, and transmit data. *Computer or related systems* can refer to computer hardware, software, peripheral devices, networks, cloud infrastructure, personnel, and associated documents (e.g., user manuals and SOPs).[22]

b. Collection and Documentation

Testing site personnel are responsible for the quality of the data. Testing site personnel should record data promptly and accurately with associated metadata.

For purposes of this guidance, *metadata* is the contextual information required to understand data, including any information used for the identification, description, or explanation of data.[23] Metadata is commonly described as data about data. Without the context provided by metadata,

[22] See Guidance for Industry *Data Integrity and Compliance with Drug CGMP – Questions and Answers* (December 2018) and guidance for industry and FDA staff *General Principles of Software Validation* (January 2002).

[23] See also Guidance for Industry *Data Integrity and Compliance with Drug CGMP – Questions and Answers* (December 2018).

the data may be meaningless. For example, the number "10" is meaningless without metadata, such as indication of the unit "mg."

Among other things, metadata for a particular piece of data could include a date/time stamp documenting when the data were acquired, units of measurement, a user identification of the person who conducted the test or analysis that generated the data, the instrument identification used to acquire the data, material status data, the material identification number, and audit trails.[24]

c. Sample Analysis

The quality of clinical studies, especially those conducted and submitted to FDA in support of application approval, depend to a large extent on the bioanalysis of participant samples from in vivo BA and BE studies. To help ensure the quality and integrity of the data derived from the analysis of samples collected during BA and BE studies, clinical testing sites and analytical testing sites, if the sample analysis is conducted at a site different from the clinical testing site, should consider including the following elements related to sample analysis listed below, which is not an exhaustive list, in the quality management system:

- Study protocols, test methods, established practices, and SOPs should be followed.
- Samples should be collected as close as possible to the times specified in the study protocol and actual sample collection times accurately documented.
- Samples should also be handled and processed as described in the study protocol and relevant SOPs.
- Key instruments and equipment, such as balances, pipettes, centrifuges, mass spectrometers, liquid chromatographs, refrigerators, storage freezers, etc., should be calibrated, maintained (including preventative maintenance), and serviced per SOPs, manufacturers' guidelines, and other requirements as appropriate. Adequate documentation should be readily available to support the above actions.
- Equipment failure should be documented and investigated to evaluate the impact on sample stability (e.g., freezer temperature failure) or data integrity (e.g., pipette or balance calibration failure).
- Logbooks or electronic databases should be maintained for temperature recordings and calibration records.
- Samples are typically shipped to the analytical site frozen with dry ice in the packaging. The addition of a data logger to such shipments is recommended because it provides temperature information in transit to the analytical site.

[24] Ibid.

- Once the analytical site receives the samples, the analytical site should document the presence of dry ice and/or data logger, and the condition of the samples.

- Freezers where samples are stored should be monitored with alarms and alarm notifications and should record temperatures at regular intervals. Temperature excursions should be addressed in a timely fashion.

The method used for sample analysis should be validated in accordance with applicable guidances and best scientific practices. This ensures the precision and accuracy of the measurements derived from sample analysis. The procedures used during sample processing and analysis should follow SOPs and analytical methods specific to the study. SOPs with prespecified objective criteria are recommended for the repeat analysis of samples, reintegration of peaks, modified integration, or reinjections.[25]

All study samples should be analyzed within the stability window established during method validation. If not possible, then additional stability data should be collected, and the validated method amended accordingly.

Documentation of sample analysis should reflect contemporaneous recording of steps and procedures consistent with ALCOA. Documentation should also allow for the reconstruction of the study.[26] In addition, audit trails should be reviewed and maintained for the analytical instruments as appropriate.

d. Data Storage

Data should be maintained with all associated metadata required to reconstruct the study activity.

Paper-based data should be stored in a secure place to prevent alteration or loss.

Electronic data should be stored in a computer or related system with limited access.

e. Data Backup

Data should be backed up according to written procedures, such as an SOP, and backup procedures should be tested periodically to ensure that the backup procedures function correctly to permit the ability to restore study data to the relevant software. FDA recommends that testing sites maintain backup and recovery logs to facilitate an assessment of the nature and scope of data loss resulting from a system failure.[27]

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[25] See the guidance for industry *M10 Bioanalytical Method Validation and Study Sample Analysis* (November 2022).

[26] Ibid.

[27] See the guidance for industry *Computerized Systems Used in Clinical Investigations* (May 2007). See also the draft guidance for industry *Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations* (March 2023). When final, this guidance will supersede the guidance for industry *Computerized Systems Used In Clinical Investigations* (May 2007) and will represent the FDA's current thinking on this topic.

For purposes of this guidance, *backup* means a true copy of the original record that is maintained securely throughout the record retention period. The backup file should contain the data, including associated metadata. The backup file should be in the original format or in a format compatible with the original format.

Backups for recovery purposes or temporary backup copies do not constitute archiving of data and metadata for the purposes of verification of the study activity.

f. Archival and Retrieval

Within two weeks after study completion (e.g., when the final study report is signed or the study has been terminated), study data (both manually recorded data and electronic data) should be archived for at least five years.[28]

Testing sites should implement controls to prevent archived data from being damaged, altered, or deleted. Further, testing site management should identify an individual who is responsible for management of the data archives.[29]

The archived paper-based or electronic data should be retrieved under the auspices of the archivist, the individual responsible for the management, operations, and procedures for archiving in accordance with established SOPs.

3. Training

All personnel who interact with BA and BE study data and perform study activities should be trained on practices and procedures of data integrity, on measures to prevent and detect data integrity issues, and on reporting errors or data integrity concerns. Training should focus on both the personnel's specific job functions, assigned tasks, and the related regulatory requirements.

Testing site management should establish procedures for identifying and routinely assessing training needs as well as documenting training and/or retraining. Under a quality management system, continued training is critical to ensure that personnel remain proficient in their operational functions and in their understanding of applicable regulations.[30]

[28] See 21 CFR 320.38, which states that each reserve sample shall be retained for a period of at least 5 years following the date on which the application or supplemental application is approved, or, if such application or supplemental application is not approved, at least 5 years following the date of completion of the bioavailability study in which the sample from which the reserve sample was obtained was used. See also 21 CFR 320.63.

[29] Expectations for data integrity should be similar, as applicable, regardless of whether the data is archived on site or in a cloud-based system.

[30] See the guidance for industry *Quality Systems Approach to Pharmaceutical CGMP Regulations* (September 2006).

4. Access and Privileges

The quality management system should include documentation that defines the access and privileges of all users, administrators, etc. FDA recommends that testing sites use access controls to ensure that personnel only have access to the functionality that is appropriate for their respective role.

FDA expects that personnel have unique log-in credentials (e.g., username, password, or access key) to access systems and only work under their own log-in credentials so that actions are attributable to a specific individual. The system should prevent users from sharing log-in credentials. When log-in credentials are shared, the specific individual who entered or modified data cannot be identified through the login. Shared, read-only user accounts that do not allow the user to modify data or settings are acceptable for viewing data.

FDA recommends that passwords to access systems be changed at established intervals.

To help prevent unauthorized access, personnel should log off the system when they leave a workstation. In addition, the system should be designed to limit the number of log-in attempts and to record unauthorized access log-in attempts and the individuals who make those attempts.

The system administrator role, including any rights to alter files or settings, should be assigned to personnel independent from those responsible for the data.[31] The system administrator role should be limited to the minimum number of personnel needed, taking into account the size and nature of the testing site. And as discussed in the Audit Trails section below, when a system administrator alters files or settings, the audit trail should record any changes made.

5. Audit Trails

It is important for testing sites to enable audit trails to document all changes made to the BA and BE study data and restrict the ability of individuals to disable the audit trails.[32] For purposes of this guidance, *audit trail* means a secure, computer-generated, time-stamped electronic record that allows for reconstruction of the course of events relating to the creation, modification, or deletion of an electronic record.[33] Audit trails should capture when, by whom, and the reasons changes were made to the electronic record.

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[31] See also the guidance for industry *Data Integrity and Compliance with Drug CGMP – Questions and Answers* (December 2018).

[32] See for example, 21 CFR part 11 and the guidance for industry *Computerized Systems Used in Clinical Investigations* (May 2007). See also the draft guidance for industry *Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations* (March 2023). When final, this guidance will supersede the guidance for industry *Computerized Systems Used In Clinical Investigations* (May 2007) and will represent the FDA's current thinking on this topic.

[33] See also the guidance for industry *Data Integrity and Compliance with Drug CGMP – Questions and Answers* (December 2018).

6. Quality Assurance and Quality Control

The quality management system should include a quality assurance program and a quality control program to manage risks associated with each element of the quality management system.

The quality assurance program should ensure the proper functioning of the processes, controls, equipment, and personnel that are part of the quality management system to ensure data integrity at each phase of the data lifecycle.

The quality assurance program should include procedures to limit users from violating the intent of the controls and mechanisms to identify data integrity breaches (unintentional and intentional) and strategies to manage and prevent recurrences.

Quality assurance personnel should be separate from and independent of the personnel engaged in the management and conduct of the BA and BE studies.

The quality control program should identify and correct data integrity weaknesses and issues in processes and controls, training and knowledge deficiencies. The quality control program should also include processes for recognizing unintentional and intentional compromised data.

When data integrity weaknesses or issues are identified, the quality control program should provide that appropriate corrective and preventative action (CAPA) be implemented across all relevant activities and systems, not in isolation. The purpose of the quality control program is to (1) collect and analyze information to identify actual and potential problems, (2) investigate problems and take appropriate and effective CAPA, (3) verify or validate the effectiveness of CAPAs; (4) communicate CAPAs to the appropriate people, (5) provide information for management review; and (6) document activities.