2 Good Documentation Practices

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Overview of Good Documentation Practices

Documentation is often the first and sometimes the only impression a regulator receives of a research group or organization. A robust documentation system serves as the foundation from which a healthy compliance program can be built and, once in place, will remain a source of first impressions during audits and inspections. The documents themselves, individually and collectively, represent the face of a company's operations.

Good Documentation Practices (GDPs) are essential in any professional setting and critical in regulated medical device, drug, and biological product environments. In general, GDPs include all written activities, processes, studies, and results associated with product development, approval, maintenance, and improvement. Good documentation serves as evidence of product development decisions and provides a basis for all activities required throughout the product's lifetime. Given the dynamics of product development and the time it may take to realize commercialization, good documentation allows consistent information transfer among parties, functional groups, and health authorities.

A sound documentation system also allows regulatory agencies to conduct a complete and efficient review of marketing applications and other communications necessary for product evaluation and approval. GDPs help regulators understand the product's history, assess the adequacy of studies, verify data integrity, and assess the appropriateness of intended use and the validity of claims about the product's safety, efficacy, and quality.

While critically important to ensure the safety of approved products, GDP compliance throughout product development should be applied from the product's conception. From prototype through clinical trials and up to postmarket surveillance, GDPs should be developed, implemented, and maintained. GDPs apply to:

- Procedures (e.g., standard operating procedures (SOPs))
- Documentation during product development (e.g., Drug Master Files or Device Master Files)
- Documentation for purposes of product clearances, approvals, and licenses (e.g., 510(k)s, Premarket Approval applications (PMAs), New Drug Applications (NDAs), and Biologics License Applications (BLAs))
- Pharmacovigilance and medical device reporting documentation
- Assembly of justification files to support an organization's decision-making process and conclusions reached
- Postmarketing documentation

Regulatory bodies do not provide a complete GDP framework. Most guidance documents and defined regulatory standards contain GDP elements, and each stage of product development has its nuances as to how documentation should be approached. Although guidance documents do not establish legally enforceable responsibilities, and their influence is limited to a health authority's current thinking on a topic, their recommendations should be applied when possible and supplemented with existing available statutory requirements. An organization should consult the expectations of all applicable regulatory authorities, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), and the World Health Organization (WHO).

Being well-versed in regulations is only the first step in creating a healthy compliance profile, producing documentation, maintaining a robust quality system, and meeting regulatory requirements. Much emphasis on GDP adherence is placed on postmarket documentation, such as medical information communications, promotional materials, and user operation manuals. These documents should not stray from the approved indications or safety and efficacy claims. Supporting documentation should be kept on file.

This chapter explores the components of GDPs. While this discussion is not exhaustive, the best efforts have been made to provide a thorough understanding of the principles and concepts necessary to develop, maintain, or improve an existing documentation system. Health authority expectations and industry best practices will continue to evolve, which underscores the importance of regularly monitoring internal systems and implementing value-added changes.

Goals of Documentation

It is best to start organizing documentation with the end purpose in mind. Documentation is essential for effective and efficient operations and serves the following purposes:

- Making internal processes and procedures clear and consistent
- Assisting in personnel training and cross-training
- Creating a reference for conducting evaluations
- Creating standards upon which continual improvements can be built
- Tracking product changes and the reasoning behind them
    - Centralizing important concepts related to business development
    - Creating a foundation for risk assessments and quality systems' maintenance
    - Incorporating global regulatory considerations, as necessary
    - Allowing internal and external product knowledge transfer
- Complying with quality and regulatory expectations
- Supporting product approval applications
- Assisting in putting the product into and maintaining it in commercial distribution

An organization must understand its documentation system's goals, define its components, review its requirements, implement its execution, train for incorporating it into organizational culture, and maintain it and its results periodically.

Basic Principles of GDPs

When developing GDPs:

- Look at the consequences of including or omitting information:
    - If information is not documented, it does not exist; retrospective documentation is not recommended.
    - Overkill in reporting minor details or repeating information may impede transparency.
    - Templates are a good start, but customization is crucial and should be specific to each organization and each internal group within an organization.
    - Do not make reviewers look too hard to verify the organization's compliance.
- Make required actions and expectations attainable:
    - Avoid requiring actions that existing personnel cannot support.
    - Budgetary constraints may exist that limit implementation of the ideal system.

    - If current operations do not allow for compliance with stated requirements, do not document them as requirements.
- Implement robust change control procedures to capture all changes made to documentation and review periodically:
    - Corrections to hand-written documentation should be made with a single line, signed and dated.
    - White out should never be used for corrections. (ICH GCP 4.9.3)
    - The reason(s) for any documentation corrections or changes should be stated.
- Remain current on quality and regulatory rules and regulations, and update documentation as needed:
    - Document compliance clearly and reference supporting guidelines and resources used.
    - If applicable, justification for any necessary noncompliance resulting from business decisions or changes in rules, regulations, or policies should be documented.
- Write clearly, using consistent practices and language:
    - Stick to technical writing basics; this is not creative writing.
    - Use established words, references, and acronyms.
    - Avoid discrepancies within and between documents. While many groups may contribute to a document, finalization should be centralized within the quality, regulatory, medical writing, and labeling group.
    - Adopt an appropriate style for each document. Bench science, manufacturing, and regulatory affairs writing styles differ and should be used as appropriate.
    - Avoid the use of arrows and "ditto" marks.
- Maintain control of contents and records:
    - Documentation should be attributable, legible, contemporaneous, original, and accurate (ALCOA).
    - Verify what is documented to the extent practicable.
    - In the event of an audit or inspection, the information trail should be clear and complete; where it may lead, or where it may fail to lead, should be anticipated and defensible.
    - Do not destroy records; keep them as accessible as possible for internal use while protecting them from public access.

Documenting Procedures

When creating documentation, the questions of what, when, why, and how should be addressed and a format created to memorialize the outcome of documented processes or procedures. With increasing emphasis being put on Quality Management Systems (QMS) and risk management during agency inspections and audits, an organization must pay careful attention to its SOP documentation. Procedures established to maintain quality operations are of little value if not followed, and when such documentation is not followed, it creates a trail of noncompliance. Any deficiency in adhering to the specifications, procedures, or recordkeeping requirements impacts an organization's compliance profile. One must adhere to SOPs, validated specifications, or other work instructions referenced within the system. The documents containing validated product specifications are most important since any deviation could compromise product quality and potentially pose a danger to consumers. If an organization has no intention of adhering to SOPs, it may be better not to have them.

Consistency, Clarity, Completeness

A primary goal of GDP is to avoid conflicting provisions, ambiguous statements, incompatible requirements, and unattainable compliance goals. Consistency is important among related documents, regulatory requirements, and agency documents so that readers can find needed information.

A documentation system often involves many cross-functional groups, sometimes with overlapping areas of responsibility. Hence, an organization may develop documents with similar business goals but diverging execution pathways. Internal communication is key when documenting roles, responsibilities,

and expectations while avoiding conflicting or inconsistent information.

A lack of specificity and detail can result in unanticipated vulnerabilities by inviting subjective interpretations. Achieving consistency involves carefully defining the terms used, abbreviations employed, and unifying individual writing styles. Also, focusing on the documentation's goal and understanding the targeted audience should be taken into consideration. Clearly delineate processes and relationships.

Writing style and language use also are important in maintaining consistency and clarity. The following questions apply:

- Is the terminology used consistently throughout the documentation system?
- Does the language cater to the intended reader's level?
- Is the document easy to read and follow?
- Do the processes and/or procedures identified lead the user to the desired result efficiently?
- Is the document's information compliant with regulatory expectations?
- Will the document's contents and relevance be easy to explain during the inspection?
- Is the information included in the document all relevant to the subject matter under discussion?

Organizations should create document inventory lists, so they are readily available to users and regulators upon request. An electronically based documentation system should include copies of historic documents and a robust change control process. Connecting the documentation and any changes to it with the training program would be optimal. The more coordinated these good documentation system elements are, the smoother the transition between product development phases and across different functional groups. The consistent capture of specifications, procedures, records, and data, and this information's accessibility are key to successful operations and a healthy regulatory compliance profile.

Completeness matters. When filling out forms or documenting results, each required element should be addressed and every blank filled with either the appropriate answer or, if not applicable, N/A. During inspections, the agency will not assume a blank space means a requirement was N/A; it will presume the requirement was overlooked. During pre-inspections, any use of "not applicable" should be scrutinized carefully and blank spaces eliminated.

Transparency and Disclosure

A culture of honesty and openness is an essential component of GDPs and achieving a healthy compliance profile. In addition to an organization's willingness to communicate, that can open the door to more efficient product review processes, audits, inspections, and compliance dispute resolution efforts. FDA emphasizes the importance of data integrity during inspections, particularly current Good Manufacturing Practice (CGMP) inspections.[1]

An organization must consider and make decisions carefully about what content should be captured in which documentation. For example, it is inadvisable to address overall product development strategy in a protocol or Investigator's Brochure, even though this information is included in an IND or background package. Internal planning and clear upper management direction are necessary, so an organization's documents remain meaningful, relevant, and applicable to its actual operations.

Identifying Documentation Guidelines and Resources

The ICH has been instrumental in the global initiative to standardize pharmaceutical product development and regulation. In realizing its vision, ICH has taken the lead on preventing duplication of efforts, reducing product development timelines, streamlining product approvals, and contributing to human health protection.

One of ICH's most important initiatives has been the creation and implementation of the Common Technical Document (CTD) for the assembly of all the quality, safety, and efficacy information for regulatory reviews in each member region. By consolidating the documentation necessary for a product to be adequately reviewed and approved efficiently, regulatory authorities, industry sponsors, and the public have benefitted.

Elements of the requirements of Good Clinical Practice (GCP), GMP, and Good Laboratory Practice (GLP) can be utilized when putting an effective GDP system into place. The following are some available resources:

- E3: Guideline for Industry Structure and Content of Clinical StudyReports (July 1996) (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073113.pdf). This guideline is helpful in developing a complete, unambiguous, and organized clinical report.
- *Guidance Document: E6(R2): Good Clinical Practice: Integrated Addendum to E6(R1)* (March 2018) (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e6r2-good-clinical-practice-integrated-addendum-ich-e6r1). This guideline outlines member countries' unified standard (GCP) for documenting, recording, and reporting human clinical trials and ensuring data integrity.
- *Guidance Document: Q9: Quality Risk Management* (June 2006) (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073511.pdf)
- Capture Source Data (ICH GCP E6 1.52)
- Maintain Adequate Records (21 CFR 812.120 (a))
- Requirements for Data Integrity
    - §211.68 (requiring that "backup data are exact and complete" and "secure from alteration, inadvertent erasures, or loss")
    - §212.110(b) (requiring data to be "stored to prevent deterioration or loss")
    - §211.100 and §211.160 (requiring certain activities to be "documented at the time of performance" and laboratory controls to be "scientifically sound")
    - §211.180 (requiring records to be retained as "original records," "true copies," or other "accurate reproductions of the original records")
    - §211.188, §211.194, and §212.60(g) (requiring "complete information," "complete data derived from all tests," "complete record of all data," and "complete records of all tests performed")
- Electronic Signature and Recordkeeping Requirements (21 CFR Part 11)
- *Design Control Guidance for Medical Device Manufacturers: Guidance for Industry* (March 1997) (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070642.pdf)
- *Guidance for Industry: Computerized Systems Used in Clinical Investigations* (May 2007) (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/computerized-systems-used-clinical-investigations)
- *Quality System Information for Certain Premarket Application Reviews: Guidance for Industry and FDA Staff* (3 February 2003) (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/quality-system-information-certain-premarket-application-reviews)
- *Guidance for Industry: Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (August 2001) (http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm200364.htm)
- *Guidance for Industry: Quality Systems Approach to Pharmaceutical CGMP Regulations* (September 2006) (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070337.pdf)
- *Guidance for Industry: Current Good Manufacturing Practice for Phase 1 Investigational Drugs* (July 2008) (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070273.pdf)
- *Guidance for Industry: Q10 Pharmaceutical Quality System* (April 2009) (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073517.pdf)
- *Guidance for Industry: Process Validation: General Principles and Practices* (January 2011) (http://www.fda.gov/downloads/

Drugs/GuidanceComplianceRegulatory Information/Guidances/UCM070336.pdf)
- *Guidance for Industry: Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products* (HCT/Ps) (December 2011) (http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatory Information/Guidances/Tissue/UCM285223.pdf)
- ISO 9001—2015; Clause 7.5; Documented Information
- Guide to GMP for Medicinal Products Part 1, Chapter 4 Documentation: PIC/S PE 009-8 (Part I)

Using Form FDA 483 Observations to Create a Good Documentation System

Form FDA 483 is issued to firm management after any inspection when an FDA investigator has observed any condition they believe may constitute violations of the *Federal Food, Drug, and Cosmetic Act* (*FD&C Act*) and related acts.[2] Often, the deficiencies cited include the lack of GDPs, i.e., design controls, clinical studies, certificates of analysis/conformance, calibrations or validations, postmarket studies, and pharmacovigilance or complaint handling.

The most constructive way to approach a Form 483 observation is to consider each deficiency cited as an opportunity to take corrective action and improve operational processes and procedures.

Some of the most recent Form FDA 483 findings can be found on FDA's website and are made available to the public through the Office of Regulatory Affairs (ORA) *Freedom of Information Act* (*FOIA*) reading room.[3] The lessons learned, preferably at the expense of other organizations, are invaluable and include the following documentation-related observations organizations should take the time to review, understand, and avoid proactively. The following are some sample findings from the *FOIA* reading room:

- The organization failed to maintain complete data from all laboratory tests conducted to ensure compliance with established product specifications and internal quality standards.
- Laboratory records did not contain all raw data generated during each test for active pharmaceutical ingredient (API) batches.
- A sample failed the purity specification limit, but the failure was not documented.
- Sample preparation information was not documented, and quality control records used to support the Drug Master File and batch disposition decisions did not include all testing results.
- None of the explanations justifies the failure to maintain complete records; neither do they support the practice of substituting repeat tests for failed results.
- The organization failed to prevent unauthorized access or changes to data and provide adequate controls to prevent data omission; no passwords are required to log into the databases, credentials are unverified, and there is no electronic or procedural control to prevent data manipulation.
- The software lacks an audit trail feature to document all activities related to the analysis performed; staff cannot demonstrate records include complete and unaltered data or verify there have been no alterations or deletions.
- The organization has no raw data for the test limits reported on the Certificates of Analyses (COAs); the release of these batches was approved without data to support that release specifications were met.
- The organization failed to ensure equipment is cleaned in a reproducible and effective manner to prevent contamination of a material that would alter API quality.
- FDA inspection revealed serious documentation practices and reported missing raw data, which compromised APIs' quality and accountability in the supply chain.
- The organization is responsible for having controls to prevent data omissions and recording any changes made to existing data, including the date of the change, the identity of the person who made the change, and an explanation or reason for the change.[4]

Building a Robust GDP System

Consider all Applicable Documentation

The following are some documents that should be considered in regulated healthcare environments:

- Research and development
  - Conception plans
  - Prototype designs
  - Specification requirements
  - Clinical study protocols
  - Investigator's Brochures
  - Investigational Review Board (IRB) and investigator communications
  - Informed consent forms
  - Case Report Forms (CRFs)
  - Investigator clinical study reports
- Sponsor narratives
- Commercialization
  - FDA presubmission communications
  - Supportive documentation for regulatory submissions
  - Manufacturing standard operating procedures (SOPs)
  - Validation and stability reports
  - Batch records
  - COAs
  - Labeling justifications and finalization
  - Regulatory submissions
- Postmarket
  - Market and launch documentation
  - Proof of compliance with acceptable practices and ISO requirements
  - Pharmacovigilance reports
  - Periodic safety updates
  - Medical information communications
  - Annual reports
  - Supplemental filings
  - Benefit-risk evaluation reports
  - Serious adverse reaction reports
  - Postmarket study requirements
  - Advertising and promotional materials and references

Good Practices for Signatures, Change Control, Validation, and Dating

If records are kept electronically, the system must be validated and backed up, and access should be limited to maintain control over any changes. Under GDPs, only the most current document may be used for any given purpose, and change control is a must. Each document should be assigned an internal control number, and revisions should be tracked. Originators, reviewers, and approvers should be identified and have appropriate qualifications to support their respective decisions.

Documentation should be dated in real-time and never pre- or post-dated. Any retrospective additions, modifications, or deletions should be signed and dated; having these changes witnessed should be considered.

The time an organization should retain any given documentation can vary, so care should be taken before destroying any records. Documents often require signatures. No document should be signed unless it is understood, and the contents are supported.

An organization's documents can be pivotal in a product liability or personal injury case, and it is possible they will be demanded during court proceedings. Likewise, any person within an organization responsible for that documentation also may be called into court. The credibility of a witness or a product's quality can be influenced greatly by implementing GDPs. In today's increasingly litigious environment, all documentation should be viewed through the lens of "could this document be explained, justified, or defended in a court of law?"

Recordkeeping, Review, Training

Understandably, organizations are focused on getting product out the door, but good documentation improves processes and, ultimately, the bottom line. An organization's quality system is based on its documentation system. Even with the best intentions, individual differences in execution or interpretation can result in inconsistencies and compromise product quality. That is why it is best to implement a GDP system at the earliest stages to minimize subjective interpretation.

Good documentation is a significant investment that may not bring immediate returns but provides important protection against internal inconsistencies, adverse regulatory actions, and legal liabilities. The human resources required to respond to an FDA 483 warrant the upfront investment in a documentation system that will mitigate communication, performance, and recordkeeping failures. Any findings of deficiencies are on the public record, available to competitors and customers alike.

Any documentation system should contain clear, consistent, and focused documents, including SOPs and training materials. Inconsistencies or ambiguities can have devastating effects on an organization's operations. Thus, documents should be reviewed periodically and reconciled with each other to minimize confusion among users. The organization should determine which are specific to its operations and customize policies and procedures accordingly. For example, processes and procedures not currently in place, even if they once were, should not be documented.

Change control will ensure all users are using the most up-to-date version of a document, and an organized change control procedure should be developed and followed. A document change control system is intended to capture changes made to existing documentation and provide a means of tracking these changes and communicating them throughout an organization.

If an organization's operations deal with medical devices and pharmaceuticals, documentation for each product type should be kept separately. Likewise, specific provisions may be necessary for documents related to an organization's pharmaceutical products if they are DEA-controlled substances, biologics, generics, etc.

Once the documentation system is in place, it should not be neglected or abandoned. Changes should be considered regularly, following schedules mandated in regulations or in conjunction with other appropriate events. In the event of an audit, the trail of the changes made, the dates of those changes, and the parties responsible for them should be identified easily, and support for those changes should be kept on file accordingly. Documenting the obvious can make short work of inspections. One test for whether updates are required is to answer the question, "can you explain how this (i.e., the subject matter of the document) all works?" It is not unreasonable for an auditor to expect a document user to explain the contents or their relevance to business operations. If a document, as written, cannot translate information to the reader to allow informed decisions to be made, reworking the document is advisable.

Training is vital to success, but such training is only as good as the documentation on which it is based. High-quality documents are the basis for high-quality training. In smaller organizations without a dedicated technical writer, consultants specializing in GDPs are available.

Good documentation not only supports and advances an organization's quality system but safeguards public health and can enhance employee retention. When everyone in an organization understands what is expected, product quality will be ensured, and the customer experience will be enhanced.

References

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