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TALE OF GOOD DOCUMENTATION IS A SALE OF PHARMA MARKETING

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ABSTRACT

One of the biggest concerns that the pharmaceutical industry constantly attempts to address is the safety of its products. GxP is a collection of regulations that aim to resolve this matter in a systematic and wholesome manner. The concept of GxP requirements in Pharmaceuticals was established by the United States Food and Drug Administration. For example, 'x' is replaced by 'D' to make it GDP which represents 'Good Documentation Practice' established by the United States Food and Drug Administration. The term itself encircles many different regulations in many different fields. Data integrity has equal importance in all departments in the pharmaceutical industry from quality control to the purchasing department. The effective control and management of documentation is a critical part of the GMP program within the organization. Documentation control is not optional – it is a legal requirement. An overview of good documentation practices applicable to those working in the pharmaceutical and healthcare sectors is presented. Specific topics for discussion include documentation fundamentals, document creation, document management, best practices in style and layout, completing documents and record-keeping, electronic records, storage, errors including error correction, and associated topics. Recommendations presented should contribute to development of an effective site documentation program.

Keywords: GDP, GMP, GXP, CAPA, FDA, TGA, EMEA, Accurate, ALCOA, ALCOA+, Audit trail, Archival, Attributable, Predating/Backdating, Backup, Computerized System, Contemporaneous, Data, Data Integrity, Effective Date, Error, Electronic Records, Electronic Signature, Hybrid System/Approach, Legible, Metadata, Data Integrity, Master Controlled Documents, Original, Paper-based Data, Post-dating, Raw Data, Records, Dynamic Record Format, Static Record Format, True Copy, Prepared by/Done by/Performed by/Analyzed by/Sampled by/Calculated by, Verified by/Checked by, Reviewed by, Review, Approved by/Certified by/Authorized by, Purpose, Responsibilities, Quality Assurance

DOCUMENT FUNDAMENTALS

There are many different types of documents found within pharmaceutical organizations, each serving a different purpose. Although there are different document types, documents can generally be placed into a small number of categories cascading down the quality system. With the types of documents and some of the errors relating to documentation use, it is useful to consider at this point how documents come together and what the basics of a document are.

This guideline highlights, and in some instances clarifies, the application of data management procedures for all GMP documents. It lays down guidelines for preparation, recording and correction of data and maintenance of records throughout the lifecycle of a document [1].

It helps to understand who, when, where, why and how to complete the relevant activities and provides evidence to show whether these have been completed as expected. Good Documentation Practices, commonly referred to as GDPs, are the guidelines that one follows in recording raw

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data entries in a legible, traceable and reproducible manner.

- Is it true?
- Is it Timely?
- Is it Accurate?
- Is it Legible?

It has been said that in the pharmaceutical industry, "If it isn't documented, it didn't happen"

Figure-1: GDP triangle

Therefore, in the pharmaceutical and medical device industry, we document to provide written proof that something happened. For this reason, good documentation practices—commonly referred to as GDPs--are critical. Records and reports related to production events represent the only official, documented record of:

- Processing a batch
- Producing a device
- The final decision to release (or reject) a batch or product
- The evidence for a corrective or preventive action (CAPA)
- An investigation of manufacturing deviations, complaints or alleged product defects
- Meeting product and quality specifications generated from test results by Records and reports, along with procedures, "tell the story" of manufactured products and devices.

In addition to regulatory requirements, it is also very important to maintain accurate records for business reasons. By maintaining clear, accurate and timely records you can take a critical look at various processes related to product manufacture with the intent of making quality, product or cost saving improvements [2].

GDPs apply to everyone who documents activities related to cGMP or current Good Manufacturing Practices by Compliance with the Food and Drug Administration's GLP, or Good Laboratory Practices, regulations (21 CFR Part 58), as well as GMP regulations for drugs and medical devices (21 CFR Parts 211 and 820) requires the use of Good Documentation Practices. GDPs are enforced by regulatory agencies such as the FDA, TGA, EMEA, Health Canada.

The principles of good documentation practices are applicable to both paper and electronic data or records filled manually or generated electronically in a GxP environment.

Accurate: Correct in all aspects or details. Accuracy is assured through equipment/instrument qualification, calibration and maintenance, validation, adherence to policies and procedures, data review, and self-inspection.

ALCOA: A commonly used acronym for 'Attributable, Legible, Contemporaneous, Original and Accurate.'

Figure-2: ALCOA attributes

ALCOA+: A commonly used acronym for 'Attributable, Legible, Contemporaneous, Original and Accurate' which puts additional emphasis on the attributes being 'Complete, Consistent, Enduring and Available'– qualities which are implicit in the basic ALCOA principles.

Audit trail: The audit trail is a form of metadata that contains information associated with actions that relate to the creation, modification or deletion of GxP records. An audit trail provides for secure recording of lifecycle details such as creation, addition, deletion or alteration of information in an electronic record, without obscuring or overwriting the original record. An audit trail facilitates the reconstruction of the history of such events relating to the record regardless of its media, including the "who, what, when and why" of the action.

Archival: Archiving is the process of protecting records from the possibility of being further altered or deleted, and storing these records under the control of dedicated data management personnel throughout the required records retention period.

Attributable: Traceable to a unique individual. 'Paper Record' refers to the initials or hand-written signature of the individual, while 'Electronic Record' refers to the log-on user ID or electronic signature of the individual.

Predating/Backdating: Entering an earlier date to a paper document (or electronic record) than the actual one on which a task was performed.

Backup: A backup means a copy of one or more electronic files created as an alternative in case the original data or system are lost or become unusable [3].

Computerized System: A computerized system can create, modify, maintain, archive, retrieve or transmit electronic records. A computerized system consists of

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hardware, software and network components which together fulfill certain functionalities. They can also be defined as a logical entity, partially or entirely controlled by computer but may also include some equipment, utilities, sensors and actuators along with the governing procedures. Examples of such a system are Building Management System (BMS), Automated Manufacturing/Laboratory System, Document Management System, etc.

Contemporaneous: Activities that are recorded at the time when they occur. Entries into GMP records are dated and/or time stamped to document when the activities occur.

Data: Data means all original records and certified true copies of original records, including source data and metadata and all subsequent transformations and reports of this data, which are recorded at the time of the GxP activity and allow full and complete reconstruction and evaluation of the GxP activity. Data may be contained in paper records (such as worksheets and logbooks), electronic records and audit trails, photographs, microfilm or microfiche, audio- or video-files or any other media whereby information related to GxP activities is recorded.

Data Owner: An individual or a team who is responsible for data generation and storage.

Data Governance: The sum total of arrangements to ensure that data, irrespective of the format in which it is generated, is recorded, processed, retained and retrieved in order to ensure a complete, consistent and accurate record throughout the data lifecycle.

Data Integrity: Data integrity is the degree to which a collection of data is complete, consistent and accurate throughout the data lifecycle. The collected data shall be attributable, legible, contemporaneously recorded, be an original or a true copy, and accurate.

Effective Date: It is the date of the document after which it becomes ready for actual use.

Error: A mistake in a document that is observed after a document was printed /executed.

Electronic Records: Any combination of test, graphics, data, audio, pictorial or other information and/or representation in digital form that is created, modified, maintained, archived, retrieved or distributed by a computer system.

Electronic Signature: The technology and controls (automated and/or procedural) established to use electronic signature within a computer system.

Good Documentation Practices (GDP): Such measures that collectively and individually ensure documentation, whether paper or electronic, is attributable, legible, traceable, permanent, contemporaneously recorded, original and accurate.

GxP: Acronym for the group of good practice guides governing the preclinical, clinical, manufacturing and post-market activities for regulated pharmaceuticals, biologics, medical devices, etc., such as good laboratory practices, good clinical practices, good manufacturing practices and good distribution practices.

GMP Documents: All types of documents which have direct or indirect impact on all aspects of the quality of drug substances/products and which are required to demonstrate or provide evidence of adherence to GMP standards and/or any other applicable regulatory requirements, are collectively referred as 'GMP documents.'

Figure-3: GXP

Hybrid System/Approach: This refers to the use of a computerized system in which there is a combination of original electronic records and paper records which comprise the total record set that should be reviewed and retained. An example of a hybrid approach is where laboratory analysts use computerized instrument systems that create original electronic records and then print a summary of the results. The hybrid approach requires a secure link between all record types, including paper and electronic, throughout the retention period of the records. Where hybrid approaches are used, appropriate controls for electronic documents, such as templates, forms and master documents, that may be printed, should be in effect.

Legible: Readable by all users of a document. Entries must be permanent and changes should be traceable to a specific individual.

Metadata: Metadata are data about data that provide the contextual information required to understand those data. Typically, these are data that describe the structure, data elements, interrelationships and other characteristics of the data record. They also permit data to be attributable to an individual.

For example, in weighing the number 8 is meaningless without metadata, i.e., the unit 'mg'. Other examples of metadata may include the time/date stamp of the activity, the operator ID of the person who performed the activity, the instrument ID used, processing parameters, sequence files, **audit trails** and other information required to understand the data and reconstruct activities.

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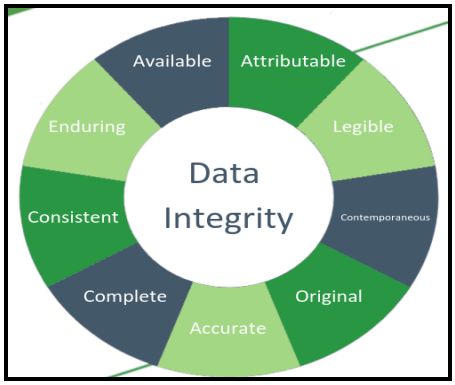

Figure 4: Data Integrity

Master Controlled Documents: All those approved documents which are usually under the custody of QA documentation cell/designated personnel and from which copies are made and issued for operational use. Examples of such documents include master manufacturing/production records, master packing records, validation/qualification/stability protocols, master SOP, specifications, standard test procedures, master templates/ analytical work sheets, etc.

Original: First capture of the data. Original records (or certified copies of the original records) must be reviewed and retained for future reference.

Paper-based Data: This includes recording formats (such as worksheets and logbooks), batch records, master records, green sheets, apex, but are not limited to these documents alone [4].

Post-dating: Entering a date for a future activity, i.e., before an activity takes place.

Raw Data: The actual information/data generated either in the form of worksheets/records, computer or instrument printouts, etc., that are result of original tests/observations/measurements/activities and forms the basis of quality decisions are collectively referred as 'Raw Data.'

Records: Records consist of any data that are collected during an operation.

Dynamic Record Format: Records in dynamic format, such as electronic records, that allows for an interactive relationship between the user and the record content. For example, electronic records in database formats allow the ability to track, trend and query data; chromatography records maintained as electronic records allow the user to reprocess the data, view hidden fields with proper access permissions and expand the baseline to view the integration more clearly.

Static Record Format: A static record format, such as a paper or electronic image, is one that is fixed and allows no or very limited interaction between the user and the record content. For example, once printed or converted to static PDF files, chromatography records lose the capabilities of being reprocessed or enabling more detailed viewing of baselines or any hidden fields.

True Copy: A true copy is a copy of an original recording of data that has been certified to confirm that it is an exact and complete copy that preserves the entire content and meaning of the original record, including in the case of electronic data, all metadata and the original record format as appropriate.

Prepared by/Done by/Performed by/Analyzed by/Sampled by/Calculated by: Such a remark records the person who is responsible for an activity by means of preparing, doing or performing the activity.

Verified by/Checked by: Such a remark records the person who is responsible for confirming or checking an activity, based on either:

- Watching or witnessing the activity being performed.
- Verifying that sequential steps were performed based on objective evidence.
- Verifying at end of the specific activity/process to ensure that the activity has been completed satisfactorily as specified in the respective GMP document.

Reviewed by: Such a remark records the person who is responsible for assessing and evaluating the activities performed, recorded, completed in the documents, based on the evaluation of supporting data/documents/references that have been attached.

Review: To look over, study or examine something with the aim of verifying the accuracy of the data.

Approved by/certified by/authorized by: Such a remark records the person who is responsible for approving GxP documents based on their evaluation of the conclusion(s).

Purpose

The purpose of this Guideline is to:

1. Describe the requirements of maintaining complete, accurate, truthful and verifiable data in all cGXP documents that are needed to be maintained as per regulatory requirements and various Governmental regulations, laws, rules and statutes/acts.
2. Describe the importance of data generation, maintaining data lifecycle, data governance and data reliability throughout the lifecycle of the document.

Responsibilities

Individuals involved in creation and execution of documents:

1. To follow the good documentation practices as defined in this Guideline and in-house policies.
2. To get themselves trained periodically on the principles of Good Documentation Practices.
3. Individuals are responsible for notifying their superiors and file deviations in cases of non-adherence to this Guideline and defined in-house policies.

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Quality assurance:

1. Quality Assurance shall be responsible for issuance, storage, retrieval and destruction of controlled documents and records.
2. To ensure that all relevant individuals are trained on the principles of Good Documentation Practices and are following them, the Department Head will ensure refresher training of the persons involved in the GMP activities.

Procedure

Approach towards record & data management:

The risk-based approach to record and data management shall ensure that adequate control strategies are in place for assurance of the integrity of GxP data. Risk mitigation with respect to record and data integrity risks associated with a process or system or throughout the data lifecycle shall be considered during preparation of risk assessment.

The approach also revolves around managing the entire document lifecycle for paper-based [5].

A comprehensive deliverable as a guidance for both manual and electronic document is designed

Flowchart 1: *Good Documentation Practices in Pharmaceutical Quality Assurance, Quality Control and Production.*

All documentation entries shall be made with indelible black ink in clear and legible handwriting.

1. Perquisition process documentation by datasheet.
2. Verification of the Document made by QA by using indelible blue ink.
3. Green ink shall be used only by QA for the issuance of BMR / BPR.
4. Do not leave any column in the record/ document unfilled. If any column in a recorded document is not applicable, write "N.A". If no comments write nil or put '---'.
5. Time should be expressed as HH.MM i.e. 2 pm should be recorded as 14.00 hrs.
6. While issuing documents and in other record books the date should be expressed as DD-MM-YY or DD.MM.YY or DD/MM/YY.
7. While approving document the date should be expressed as DD-MM-YYYY or DD.MM.YYYY or DD/MM/YYYY.
8. If any page(s) left blank, draw a line across the page from left top to right bottom of the page and write "CANCELLED" / "N.A." (Not applicable) across the page and sign with the date.
9. If an entire page/ paragraph is has to be canceled from a document, QA counter sign is required.
10. No pencil entries are allowed.
11. Do not use correction fluid in any of the document.
12. All personnel shall avoid errors during data entry.
13. In case an entry error occurs, the same shall be corrected as described below.
14. Do not overwrite the wrong entries. Cross it out with a line permitting the reading of original entry. Clearly write the correct entry near the cross out.
15. Initial / Sign and put the date, on which the correction was made. Wherever appropriate, the reasons for correction shall be recorded.
16. If the correction is made on a date after the date of original entry, it must be corrected as mentioned above and counter signed and dated by the supervisor or QA.
17. If an entire line/ paragraph/ page to be deleted from a sequential record (e.g. log book or stock card) the following steps to be taken.

i) Cross out with a line

ii) Write a comment explaining the reason for deletion near the cross out.

iii) Initial/ sign and put the date, on which the correction was made.

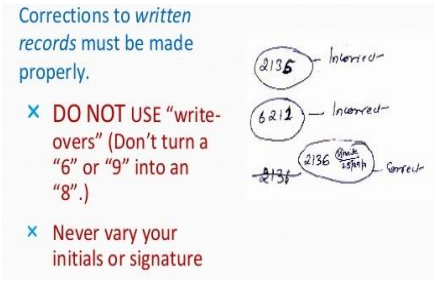

Figure-5: Manual data interpretation

Good documentation practices for manual/paper documentation:

1. Design/generation of manual/paper-based documentation

1.1 All documents must be accurate and written in a manner that prevents errors and ensures consistency.

1.2 Documents shall have unambiguous contents; the title, nature and purpose shall be clearly stated.

1.3 Pages in the master document shall be numbered as X of Y (e.g., Page 2 of 20).

1.4 Full text spelling with the abbreviations in brackets shall be used for the first time.

Abbreviations may be used in place of full text spelling in the remaining part of the document.

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1.5 Definitions shall be included in the document for reference. This is most effectively done by including the definitions in a table format, at the start or end of the document.

1.6 Reproduced documents shall be clear and legible. The reproduction of working documents process. A document reproduced from the original should be appropriately identified,

e.g., name or identity of the person, date, time and number of copies made.

1.7 Records shall be made or completed when any action is taken and in such a way that all significant activities concerning the manufacture of pharmaceutical products are traceable.

If documents are to be used together, e.g., a SOP and a form, then each shall reference the other.

1.8 All documents shall have the signature and date of the person who prepared, reviewed and approved the document.

1.9 All documents shall have an effective date and a review period if applicable.

1.10 Master formulae and detailed procedures (SOPs) relating to the system in use shall be available and the accuracy of the records shall be checked. Respective SOPs shall be followed while preparing the documents.

1.11 Changes or revisions to documents shall be assessed to check the impact and handled through a review and approval process of change management.

1.12 The roles of reviewer and approver shall be defined.

1.13 All documents shall have a unique identification number (including the version number).

1.14 The use of uncontrolled documents shall be prohibited by local procedures.

1.15 The use of temporary recording practices, e.g., scraps of paper, shall be prohibited.

2. Review and approval of documents

2.1 Review of GMP documents

2.1.1 Documents within the Quality Management System shall be regularly reviewed and kept up to date.

2.1.2 To ensure that the information is correct and accurate, documents and records shall be reviewed by someone who has performed the task and has proper knowledge.

A signature and date by the reviewer shall confirm that a review has taken place.[6]

2.1.3 When a document has been revised, a system shall exist to prevent inadvertent use of the superseded version.

2.1.4 Superseded documents shall be retained for a specific period of time.

2.1.5 Unsigned or incomplete documents or records shall not be used to perform any task or considered as evidence of a completed task.

2.2 Approval of GMP documents

2.2.1 Documents shall be approved, signed and dated by the appropriate responsible persons. No document shall be changed without authorization and approval.

2.2.2 All master documents shall have effective date, approval date and current version number.

2.2.3 Training on the document shall be planned only after approval of document and shall be completed before the effective date.

2.2.4 All GMP documents shall be approved by Quality Assurance.

3. Issue of GMP documents

3.1 The formats or records associated with the activity shall be part of respective SOPs.

3.2 Master copies of controlled documents (paper-based and electronic) must be stored in a secure manner and accessible only to authorized individuals.

3.3 Records shall be maintained for issuance and retrieval of formats with traceability of the person who issued the document and the date and time when it was issued.

3.4 Appropriate procedures shall be in place to ensure that data is recorded in the Controlled Data Sheet or Current formats issued by Quality Assurance.

3.5 Appropriate procedures shall be in place to ensure that the system of controlled issuance of bound and paginated notebooks with sequentially numbered pages and blank formats is in place

to allow persons to detect missing or skipped pages and help in accountability of issued formats.

3.6 Any document printed for review/reference purpose must have suitable watermarks or stamps to have adequate control on the document. This shall be signed and dated by the person who has printed the document.

3.7 Appropriate procedures shall be in place to control distribution of documents within the organization.

3.8 Reconciliation of issued documents shall be performed and recorded in the respective issuance log.

4. Recording/data capture on GMP documents

4.1 Recording of data on GMP documents

4.1.1 Handwritten entries shall be made in a clear, legible, indelible manner. Where documents require the entry of data, sufficient space shall be provided for such entries and they shall be laid out in an orderly fashion and be easy to check.

Data overwriting is prohibited.

Where the ink fades or smudges during recording of data, the faded or smudged entries shall be struck out and a new entry must be made by giving appropriate justification with signature and date.

If data has been erroneously struck off, appropriate justifications shall be provided along with signature and date.

4.1.2 Indelible ballpoint pen shall be used to record data. Pencil or erasable or water-soluble ink pen shall not be used to complete the GMP documents.

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4.1.3 Use of white ink, correction fluid or sticky notes (e.g., Post-it notes) to correct the entry in GMP documents shall not be permitted.

4.1.4 Entries shall always be recorded at the time of activity in a contemporaneous manner.

Date and time of completion of activity shall be recorded in a predefined standard format as found suitable by the firm. The format of date and time should remain consistent throughout all the documentation formats across the firm. In case a printout generated by equipment/instrument/system has a different format, it shall be converted to the standard format while entering in logbooks/GMP documents.

4.1.5 It shall be ensured that the time displayed in all the systems, computers and clock of a manufacturing unit is synchronized by an authorized designated person or department.

4.1.6 In case operations are continued from one shift to another where the dates are different, the date shall be recorded against the timing in the date column.

4.1.7 All numerical/actual values displayed on or observed from the instrument/equipment shall be entered with appropriate units of measure (UOM) as applicable (such as Kg, gm, mg, °C, Psi) in a manner that assures no ambiguity to a second person.

4.1.8 Data shall be recorded only in the format duly issued and approved by Quality Assurance.

4.1.9 Logbooks shall be kept for major or critical analytical testing, production equipment, areas where product has been processed and other usage logs.

4.1.10 Entries in the logbooks shall be made in chronological order including the dates; such entries shall identify the people who carried out these operations. Entries shall never be pre-completed.

4.1.11 Data recording shall be done by trained and authorized persons.

4.1.12 Data shall be recorded exactly as it is displayed on the respective equipment panels.

4.1.13 The numerical value of the data shall be recorded as is (i.e., with all decimals) as it appears in the displays.

4.1.14 Numeric rounding practices and recording of significant figures after calculation shall be predefined and followed.

4.1.15 Unusual observations during the activity shall be recorded, signed and dated. The same shall be reported to the area person in-charge and QA.

4.1.16 If any observation/signature/date is to be repeated, the same shall be rewritten.

Markings such as Ditto (--"--), " as above" or "do" shall not be used.

4.1.17 Records should capture the actual and clear observations. Shortcuts such as putting remarks like OK/Not OK, Comply, Done. etc., shall not be acceptable. However, in certain formats like checklists, where the activity is to be conducted and recorded,

"Yes" or "No" shall be written indicating whether the activity was performed or not performed. The same shall be signed by the person executing the checklist.

4.1.18 Bracketing, such as ( ), in any form shall not be done to group or to provide the same answer to multiple check points. For example, remarks as shown below are not acceptable:

Operation done by Checked by

DEF

ABC XYZ

GHI

4.1.19 Data recorded in GMP documents shall always be signed and dated.

4.1.20 No employee shall be permitted to sign for another member of the staff unless authorized. Signatures shall never be forged.

4.1.21 Pre-dating or post-dating of GMP documents is not an acceptable practice.

4.1.22 Scratch papers, loose papers or "Post-it" notes shall not be used to record the data.

4.1.23 Raw data/print outs or supplements generated during the activity shall be signed, dated and attached with relevant record. Printouts made on thermal paper from an instrument/system shall be photocopied and both the copies shall be secured along with the report. The photocopy shall be marked as "COPY OF ORIGINAL" or "COPY OF TRUE COPY" as appropriate on the photocopy along with initial and date. Information on thermal paper should not be taped over, since the tape will cause the data to fade rapidly.

4.1.24 Blank/unused space in the document shall be struck through with a single line with signature and date to ensure that a record cannot be altered on a later date.

4.1.25 In case of blank fields wherein striking out is not feasible, "NA" shall be mentioned.

This shall indicate that the blank space was not skipped or forgotten while making entry.

4.1.26 Where there is a space constraint in making a manual entry in the GMP documents, an additional page can be included as attachment/annexure which shall be numbered with a cross reference in the mother record to which it is attached. The attachment/annexure shall bear paginated with sequential numbering (e.g., Page 1 of 2 or Pg. 1/2 and so on).

4.1.27 In the case of modifications to a document before final approval, an additional page can be attached to the original document as attachment /annexure with the changes made, which shall be cross-referred to the original/mother document. The concerned department involved in the approval process shall be informed and involved in the signatory cycle.

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4.3.3 Any corrections to a signed-off document shall be routed through error ratification procedure and kept along with original document [7].

4.3.4 Missing entry in the GMP documents for non-retrieval data shall be handled through deviations procedure, for example, an operator has missed the reading of the drying temperature during the operation where there is no automatic data recording mechanism in place.

4.3.5 If during review, any entry or signature is found to be missing and if a suitable evidence for execution of that entry or presence of that person in that process is available, then a symbol (*, @, #) shall be done at the place where entry/signature is missed and at the bottom of that page a remark shall be mentioned with the correct entry and reason which shall be initialed as on current date.

Example 1: If a temperature reading was missed out in a record, for which there is supporting electronic data indicating the temperature reading, then the same shall be handled by the above-mentioned procedure. The printout of the temperature reading generated from the system shall be attached with the original record as evidence.

Example 2: If the review reveals missing signature of a person in a record, and there is sufficient evidence that the concerned person was available during the operation, the same shall be handled by above-mentioned procedure with evidence retained with the record.

4.3.6 If an error is observed in the master documents, it shall be handled through error ratification procedure or change management, depending on the impact of error.

4.3.7 The nature of corrections made shall be reviewed to analyze if they can be incorporated on a permanent basis.

4.3.8 In case a data entry error is observed in electronic GMP documents (e.g., transcriptional entry errors), a documented procedure shall be put in place (e.g., having a log to maintain data entry errors).

5. Review and reconciliation of GMP documents

5.1 Error Ratification

5.1.1 The errors identified in documents shall be notified to the head of concerned department who owns/is responsible for the document.

5.1.2 The error identified shall be verified by the concerned department head to initiate an error ratification form as per Annexure 2.

5.1.3 An appropriate numbering system shall be in place for sequential numbering, logging and traceability of error ratification forms.

5.1.4 Errors which lead to confusion or complete deviation from the actual meaning of the intended use of the document or have direct impact on product quality shall be routed through deviation procedure.

5.1.5 The details of error and the document in which the error was identified shall be recorded as per Annexure 2 and the impact of error shall be assessed.

5.1.6 Methodology of rectification of error shall be recorded (e.g., updating the documents, trainings, etc.).

5.1.7 If a correction is required in documents submitted to a regulatory body or a customer, they shall be routed through Regulatory Affairs.

5.1.8 Upon approval and verification by Quality Assurance, the changes shall be made to the document as per the defined methodology for rectification of error.

5.1.9 The original error ratification form shall be maintained by Quality Assurance and a photocopy of the same shall be attached and retained with the respective document.

5.1.10 Quality Assurance shall review and close the error ratification form. Where required, CAPA shall be logged.

5.1.11 Justification for delay in closeout of the error ratification form shall be provided.

5.1.12 A limit should be set on the error ratification forms allowed to be raised for one document. (e.g., not more than 3 Error Ratification Forms shall be allowed for a master document).

5.1.13 Any change in input quantity, numerical value/formula, change in calculation, yield, and addition/deletion of processing step should be routed ONLY through change control procedure.

5.2 Cancellation of GMP documents

5.2.1 Cancellation of records shall be handled through change management procedure, capturing the reason for cancellation and signed by area person in-charge and Quality Assurance.

5.2.2 The data shall be transcribed with proper justification. The voided data shall be cross referenced in the new document by attaching the original document for traceability.

5.3 Missing Documents

5.3.1 If any executed record has been lost or is not traceable then it shall be handled though a deviation procedure.

5.3.2 In case of torn/damaged page of document or record, the following procedures should be followed:

5.3.2.1 If any document or record has been torn/damaged during handling, all portions of the relevant pages shall be joined with transparent cello tape and a photocopy of the page shall be taken and signed off with justified reason in the footnote of the document, treating it as original document. It is necessary to retain the original pieces /portions of such pages along with a photocopy of the document.

5.3.2.2 In case of spillage on any document thereby making the entry illegible, this shall be brought to the notice of the department head and further action shall be taken based on decision by Quality Assurance. An incidence report shall be filed and the re-issuance of the format shall be requested to Quality Assurance. The spoilt copy shall be retained along with the new copy.

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6. Storage and retrieval of GMP documents

6.1 Retention of Document

6.1.1 There shall be pre-defined retention periods for different sets of documents.

6.1.2 An inventory of documents within the quality management system should be maintained.

6.1.3 It shall be clearly defined as to which record is related to each manufacturing activity and where this record is located.

6.1.4 The maintenance of paper records shall be such that it should be easy to archive the records at any time during the record lifecycle.

6.1.5 Secure controls must be in place to ensure the integrity of the record throughout the retention period and validated where appropriate.

6.1.6 For other types of documentation, the retention period will depend on the business activity which the documentation supports. Critical documentation, including raw data (for example, relating to validation or stability) which supports information in the Marketing Authorization, shall be retained whilst the authorization remains in force.

6.1.7 It may be considered acceptable to retire certain documentation (e.g., raw data supporting validation reports or stability reports) where the data has been superseded by a full set of new data.

6.1.8 Justification for this shall be documented and shall take into account the requirements for retention of batch documentation; for example, in the case of process validation data, the accompanying raw data shall be retained for a period at least as long as the records for all batches whose release has been supported on the basis of that validation exercise.

7. Revision of GMP documents

7.1 All revised documents shall mention its revision history.

7.2 Periodic reviews of controlled documents and forms shall be done as per approved procedure and shall be handled through a change approval process.

7.3 Only authorized personnel shall revise the documents.

7.4 Document revisions shall always be version controlled and only the latest version shall be used at any point in time.

7.5 Versions of documents created shall be managed through logbooks.

7.6 Revised documents shall have date/time stamped and shall also be signed by respective personnel.

7.7 All revisions of GMP documents shall be handled through change approval process.

8. Destruction of GMP documents

8.1 A record shall not be destroyed before its stated retention period or validity without appropriate justification and consultation with Quality Assurance.

8.2 Any approved or under approval GMP document shall not be discarded or destroyed without the appropriate stamp authorizing cancellation/obsolescence.

8.3 Any draft SOP, reference document or record printed for review/reference purpose with a watermark "Draft' can be destroyed. These shall be destroyed by appropriate means like shredding. Documents which are under approval or review shall be stamped appropriately indicating that it is submitted for correction.

8.4 Labels used at different process levels shall be destroyed by defacing with a cross "X" mark on it (e.g., status label of equipment, cleaning labels, visual inspection status labels, leak testing status label, product quarantine and release labels, etc.).

Good documentation practices for electronic documentation:

1. Design/generation of electronic documents

1.1 Appropriate roles shall be defined with relevant privileges on the electronic system to ensure that there is no overlap of roles.

1.2 Access to the master templates shall be controlled.

1.3 Access control shall be provided either through biometric or two-level controls (unique username and password).

1.4 Process controls for creating and updating versions should be clear and practically applied.

1.5 Document design should allow entering of data contemporaneously.

1.6 Data (and records for storage) may be recorded by electronic data processing systems or by photographic or other reliable means.

1.7 Data processing methods should be approved, identifiable and version controlled.

1.8 For hybrid systems (part manual and part electronic) a clear white paper shall be produced which is version controlled and describes the systems which are electronically controlled with a roadmap for the future.

1.9 For activities where an electronic record is generated in addition to a paper document, it shall be determined in advance whether the electronic record or paper record is used in any decision-making process.

2. Review and approval of electronic documents

2.1 Review of GMP electronic documents

2.1.1 For data generated from a computerized system, regular review of audit trails shall be conducted to identify incorrect processing of data and prevent incorrect results from being reported. It shall be ensured that both administrative audit trail and business workflow related audit trail are reviewed for each system/application.

2.2 Approval of GMP electronic documents

2.2.1 All system-based documents shall be approved by Quality Assurance.

2.2.2 Review and approval flow of documents shall be designed.

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2.2.3 Document review and approval should be managed through change control.

2.2.4 Approval with electronic signatures should have appropriate date/time stamps.

2.3 Signing of electronic GMP documents

2.3.1 The meaning of signature (manual or electronic) shall be communicated to the personnel involved in signing off GMP documents.

2.3.2 Signing any GMP documents (manual or electronic) indicates that the person is in agreement with the information provided or conclusions in the record and is accountable for the documents he is signing. (Refer format Annexure 1 for Electronic Signature Accountability Certificate).

2.3.3 Equipment/instrument that are access-controlled shall have individual ID and password so as to ensure the capture of attributable records. If individual ID and passwords are not available, all activities associated with those equipment shall be documented for the person who performed the independent activity and when.

2.3.4 Use of stored digital images of a person's hand-written signature to sign a document shall not be permissible.

2.3.5 Electronic signatures shall be executed to electronically sign off a record, which shall be unique to the individual and shall not be reused by or reassigned to anyone else.

2.3.6 An electronic signature must be based on a combination of an identification code (e.g., username) and a password.

2.3.7 A signed-off electronic record shall contain information that indicates the following:

—— Printed name of signatory or ID

—— Date and time when signature was executed

—— Meaning of signature (such as review, approval, responsibility)

2.3.8 Application of electronic signature to an electronic record must be done at the time the corresponding action or activity is performed and applies to current contents of the record.

2.3.9 Non-biometric electronic signature shall employ at least two distinct identification components such as identification code or password.

2.3.10 The uniqueness, security, and authenticity of electronic signatures shall be validated during computer system validation.[8]

2.3.11 A hybrid approach may be used to sign electronic records when the system lacks features for electronic signatures. For example, a single-page controlled form would be handwritten signature. This paper record with the hand-written signatures shall then be securely and traceably linked to the electronic data set, either through procedural means or technical means, such as embedding the scanned image of a certified true copy of the signature page into the electronic dataset.

3. Issuance (control) of electronic documents

3.1 Issuance of GMP electronic documents

3.1.1 Automated mail communication should reach the users upon document version changes.

3.1.2 Controlled documents shall be issued through document management system.

3.1.3 Controlled documents shall have an "issued by" date and time stamp along with name of the person responsible for their dissemination.

3.1.4 Authorized personnel shall update the master documents in document distribution system.

3.1.5 e-BMR/BPR shall be downloaded with process order.

3.1.6 Date and time stamped audit trail records shall be available for document issuance.

3.1.7 Periodic audit trail/system audit trail reviews must be conducted.

3.2 Controls on Electronic Data

3.2.1 Master documents should be stored in a manner which prevents unauthorized changes.

3.2.2 Appropriate controls for electronic documents such as templates, forms, and master documents shall be implemented. Appropriate controls shall be in place to ensure the integrity of the record throughout the retention period.

3.2.3 If documentation is handled by electronic data-processing methods, only authorized persons shall be able to enter or modify data in the computer, and there shall be a record of changes and deletions; access shall be restricted by passwords or other means and the entry of critical data shall be independently checked.

3.2.4 The use of shared and generic log-on credentials shall not be permissible, since it is essential that personnel actions documented in electronic records can be attributed to a unique individual.

3.2.5 Where adequate technical controls are not available or feasible in legacy electronic systems, combinations of paper and electronic records shall be used to meet the requirements to attribute actions to an individual.

3.2.6 Users shall not have the ability to amend or switch off the audit trails or have access to alternative means of providing traceability of user actions.

3.2.7 Where a computerized system lacks computer-generated audit trails, persons may use alternative means such as procedurally-controlled use of logbooks, change control, record version control or other combinations of paper and electronic records to meet GxP regulatory expectations for traceability to document the what, who, when and why
of an action.

3.2.8 Business process owners and users shall not be granted system administrator privileges, at any system level (e.g., operating system, application, database), which

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will enable them to change settings to overwrite, rename, delete, move data, change time/date settings, disable audit trails and perform other system maintenance functions that turn off the GDP controls for legible and traceable electronic data. Such permissions may be given to persons fully independent of the persons responsible for the content (e.g., IT, metrology, records control, engineering, etc.).

3.2.9 GMP documents stored electronically shall be protected by backup transfer on magnetic tape, microfilm, paper print-outs or other means. Backup activities shall be conducted according to a predefined schedule and such procedures should be documented.

3.2.10 Data saved electronically and respective paper prints shall be checked so as to ensure that the printed data are accurate and identical to the electronic data.

3.2.11 The ability to restore and read the backup electronic data should be verified as per a predefined schedule.[9]

4. Recording/data capture on electronic documents

4.1 Electronic log must be maintained for document usage. In case of electronic data, the computer systems shall have adequate controls in order to prevent alteration of time/date stamps.

4.2 Data shall be entered electronically.

4.3 The system shall prompt for error messages for missing data.

4.4 Exceptions shall be generated for out-of-limit results.

4.5 All entries shall be captured in an audit trail with date and time stamp and name of the personnel.

4.6 Executed documents shall be released by Quality Assurance.

4.7 It shall be ensured that the time displayed in all the systems, computers and clock of a manufacturing unit is accurate and synchronized.

4.8 Equipment/instrument should be connected to electronic system for real time data transfer.

4.9 Electronic master production and control record must be validated to run the workflow correctly.

4.10 Audit trails that capture changes to critical data should be reviewed with each record before final approval of the record.

4.11 E-BMR and LIMS shall be designed to automatically save the data after each separate entry like paper record.

4.12 In case of electronic records, the configuration settings or SOPs, as feasible, shall enforce committing of electronic data to durable media at the time of the activity and prior to proceeding to the next step or event in the sequence of steps and events.

4.13 When e-logbooks are maintained, an alternative mechanism shall be available to handle situations in case the e-logbook is not working.

4.14 Electronic data generated from instruments shall be stored in a defined path of PC/Server. The data storage path shall be defined.

4.15 File and project naming conventions are defined by procedure and should be followed accordingly.

5. Review and reconciliation of electronic documents

5.1 Cancellation of GMP electronic documents

5.1.1 Cancellation of electronic records shall be allowed only in rare cases supported by suitable justification with the approval of Quality Assurance.

6. Storage and retrieval of electronic documents

6.1 Storage of electronic documents

6.1.1 Privileged personnel should have access to the document archival system.

6.1.2 Document shall be stored in suitable media/server, labeled and stored in designated folders for easy retrieval.

6.1.3 Electronic data shall be stored in suitable conditions, free from environmental, vibrations and magnetic fields.

6.1.4 Data modification or deletion shall be tracked through an audit trail.

6.1.5 An electronic log shall be maintained for document archival.

6.1.6 Contingency plans and procedures for disaster management shall be in place for data security.

6.1.7 Data recovery shall be done periodically based on documented procedures.

6.1.8 Reconciliation log shall be maintained for archived data and shall have date/time stamp.

6.2 Retention of electronic document

6.2.1 If an electronic record is copied to another system, the metadata including the audit trail and electronic signature is not required to be copied, but must be retained in the original system. If original system is no longer maintained, the metadata and audit trail and electronic signature must be migrated along with the electronic record.

6.2.2 Secure controls must be in place to ensure the integrity of the record throughout the retention period and validated where appropriate.

Document Errors

Common documentation errors that commonly appear in FDA warning letters and reports from other regulatory authorities include

Documentation not contemporaneous

- Use of ditto marks
- Use of signature stamp
- Incorrect ink used for entries causing illegible data when a substance was spilled
- Logbook corrections failed to identify person who made the changes
- Obscured original data
- Use of pencil
- Inaccurate records
- Sample sequence table and audit trail not documented (to draw on the commonly used phrase: “if it is not documented, it didn’t happen”)
- Handwritten changes not dated

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• Write-overs, multiple line-through, and use of "white-out" or other masking device.

The most common GMP citation occurs with correction of errors when information is recorded.

Correction of documentation errors should include:

• Draw a single line through the error,
• Make the correction next to the error,
• Write an explanation for the error,
• Sign and date the correction.

It is recommended that these common errors are highlighted in training on the creation and use of documentation.[10]

Responsibilities

GMP requires that the management of each facility defines responsibility for origination, distribution, maintenance, change control, and archiving of all GMP documentation and records within a given department or unit. At the departmental level, document owners are required to ensure acceptability of all aspects of documentation and records management. The documentation systems should be audited periodically by the quality assurance function. Despite control systems and application of the audit process, regulators frequently cite documentation errors and poor practices at inspection

Document Control

Further considerations regarding the system controlling documentation include:

• Documents should be available at point of use
• Masters, including electronic versions, are held under control
• There is control over format
• There is a system for changes, approval, and re-issue
• There is control of documents of an external origin.

The majority of these requirements also make up the elements of the "documentation lifecycle"

— From document creation, through its use, to its storage and archiving, and then to its eventual retirement and possibly replacement by a revised version. The control of documents necessitates the following steps:

1. Documentation creation

• Documents must be contemporaneous with the event they describe
• Documents must not be handwritten (except for handwritten entries)
• When electronically produced, the documentation must be checked for accuracy
• Free from errors
• For some types of data, the documentation must be in a format that permits trend evaluation

2. Document approval

• Documents must be approved for use. They must be approved, signed, and dated by appropriate authorized personnel.

3. Handwritten entries

• Adequate space needs to be provided for expected handwritten entries
• Handwritten entries must be in indelible ink
• Critical entries must be independently checked (second person verified)
• No spaces for handwritten entries should be left blank. If unused, they are crossed out or "n/a" (or similar text) entered
• Ditto marks or continuation lines are not acceptable
• A stamp in lieu of a handwritten signature is not acceptable.

4. Document copies

• Copies need to be clear and legible
• Errors must not be introduced
• Documents should be regularly reviewed and kept current,
• Documents should be retained and readily available for audits
• Archived documents must be retrievable for the appropriate duration
• Electronic document management systems must be validated
• Electronic records must be backed up.

5. Document modification

• Handwritten modifications are signed and dated
• Altered text should not be obscured (e.g., no obliterating the text through crossing-out)
• Where appropriate, the reason for alteration must be noted (for example, "e.e." is a common abbreviated reason, indicating "entry error"),
• Controls exist to prevent the inadvertent use of superseded documents

Electronic versions should only be modified by authorized personnel

• Access to electronic documents must be controlled by password or other means. A history (audit trail) must be maintained of changes and deletions to electronic documents. Well-designed documentation and appropriate documentation are paramount. It is necessary to document every aspect of the process, activities, and operations involved with drug and medical device manufacture. If the documentation showing how the product was made and tested (which enables traceability and, in the event of future problems, recall from the market) is not correct and in order, then the product does not meet the required specification and could be considered to be adulterated.

Good documentation practice GDP is a systematic procedure of preparation, reviewing, approving, issuing, recording, storing and archival of any document.[11]

The importance of documentation:

As per GMP documentation control "If it is not written down, then it did not happen". The document provides information on when, where, who, why and how to

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complete the task. The document provides evidence proving that the tasks have been completed as they should be.

Basic requirements of GDP:

1. Always record the entries at the time of activity simultaneously.
2. Always record date with the signature in GMP records.
3. Always use an indelible ballpoint pen to record data in GMP records.
4. Always enter the data directly into the GMP records in the English language.
5. Never use a pencil or erasable or water-soluble ink pen to complete the GMP records.
6. Never use white ink or correction fluid to correct the entry in GMP records.
7. Never sign for someone else on any document. Only sign for the work that you have performed yourself.
8. Never backdate GMP records.
9. Never discard original raw data of any kind.
10. Never use scratch papers, loose papers or "post it" to record the data.
11. Never discard or destroy any GMP record unless retention period expiry is reached.
12. Documentation and records used throughout the manufacturing process, as well as supporting processes, must meet the basic requirement of
GDP.

List of such documents is provided below (List is not limited):

Batch manufacturing records
Bill of Materials
Specifications
SOPs
Protocols
Test methods
Checklists
Forms / Log sheets
Training assessments
Certificate of Analysis
Technology transfer document
Validation documents
Maintenance records
Calibration records

General requirements

Below mentioned requirements should be applied to all the GMP documentation within the GMP environment.

A. Clearly written documentation:

● All documents must be accurate and written in a manner that prevents errors and ensures consistency.

● If documents are to be used together, e.g. a SOP and a form, then each should reference the other.

● Ensure there is traceability between two or more documents/records using formal document numbers or record identification.

B. Using indelible ink:

● All records must be filled out in indelible BLACK or BLUE ballpoint pen for long-term legibility.

● Do not use pencil or ink that can be erased.

C. Legible handwritten Entries:

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● A document is unusable if it cannot be read, so care must be taken to ensure that handwriting is legible. All entries must be made at the time the
tasks are performed and should be legibly signed and dated.

● The same is true for electronic documents and records – language should be clear and unambiguous.

D. Reviewing and approving:

● To ensure that the information is correct and accurate, documents and records should be reviewed by someone who has performed the task and
has the proper knowledge. A signature and date by the reviewer/approver confirm that a review has taken place.

● Unsigned documents or records are incomplete and should not be used to perform any task or considered as evidence of a completed task

E. Employee signatures:

● Handwritten signatures must be unique to the individual and listed within the signature register to ensure that the signature is traceable to the
concerned employee (or contractor).

● Any employee should not be permitted to sign for another member of staff unless delegated. Signatures must never be forged.

● The management of the signature record should be governed by a procedure and routinely reviewed so that it remains current – the new employee
should sign the signature register during induction, the signature register must indicate the date employee exit.

Preparation of documents

1. Clear and concise titles should be used for headings, tables, graphs, etc.
2. Pages in the master document should be numbered as X of Y.
3. Full-text spelling with the abbreviation in brackets should be used for the first time. The abbreviation may be used in place of full-text spelling in the remainder of the document.
4. All documents should have the signature and date of the person who prepared the document, reviewed the document and approved the document.
5. All master documents should have an effective date, approval date, and current version number.
6. Respective SOPs should be followed while preparing the documents.
7. Words that everyone can understand should be used. Unfamiliar words reduce the reader's understanding of

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what is written. Definitions of abbreviations should always be included in the document for reference. This is most effectively done by including the definitions in a table format, at the start or end of the document.

8. Ensure that the contents of the document are not squeezed into a smaller area just to limit page numbers. Documents with small margins and no spaces between paragraphs and headings can be difficult to look at, hard and slower to read. Space the contents out so that the type/font is easy to read for all users.

9. When creating a document, consider the context in which the document may be used in the future and whether the reader has enough background information.

10 People remember information best when there is a strong visual prompt, such as a diagram. When the document has to be lengthy, consider using tables to structure the information for the easy understanding of the reader.

11. Training of the document should be planned only after approval of the document and shall be completed before the effective date.

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Issuance and retrieval of GMP records

1. All the forms associated with the activity should be part of respective SOPs.

2. QA maintains the list of GMP impacting forms and its associated SOP.

3. Records for issuance and retrieval of such forms should be maintained.

Recording the time and date in GMP records

1. Time should be entered in 24:00-hour cycle. Record the time in HH: MM format. For Example 11:05 AM should be written as 11:05 and 11:05 PM should be written as 23:05.

2. The date should be entered in DD.MM.YY format. For example, 27th July 2013 should be written as 27.07.13. Place "0" before the digit if the digit is less than 10 for the recording of date.

Data recording in the GMP records

1. Date and time should be recorded in GMP records as mentioned above.

2. Data should be recorded only in the format duly issued and approved by Quality Assurance.

3. Entries in the logbooks should be made in chronological order. Entries should never be pre-completed.

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4. Data recording should be done by trained and authorized personnel.

5. Data should be recorded as it is displayed on the respective equipment panel.

6. Unusual observation during the activity should be recorded, signed and dated. Same should be reported to area person-in-charge and QA.

7. If any observation/signature/date are to be repeated, the same should be rewritten. Ditto (----"---) marking or "as above" or "do" should not be used.

8. Manual entries should be reviewed and signed by the second person for accuracy and completeness.

9. Raw data/printouts generated during the activity should be signed at the left bottom with the date and should be attached to relevant records.

Printouts made on the thermal paper should be photocopied. Thermal paper copy along with photocopy should be attached to the concerned record.

Correction of entry in GMP records

1. Incorrect entries in GMP records should not be overwritten or blocked to make it unreadable.

Always use a single strike outline (For example Incorrect Entry) to mark the incorrect entry in such a manner that entry remains readable.

2. Correct entry should be written near to the strikeout entry. Person correcting the entry should put the initial signature and date along with the corrected entry. Only the person who made the original entry and strikethrough should make the correction. If this is not possible, notify QA.

3. The reason for correcting the entry should also be documented on the record. In the case of space constraint in the document, the reason for correction should be mentioned in the footer of the record with (*) sign.

Handling of missing entry in GMP records

1. Entries in the GMP records should be done contemporaneously with the activity. However, the procedure mentioned below should be followed in the exceptional case of missing entry in GMP records.

2. Missing entry in the GMP records can be re-entered later if the data are retrievable. (For example start time of blender is missed by the operator, however, the entry for the same is mentioned in the equipment usage log)

3. In such a case, an entry should be made with a clear indication of the date when the activity was performed and the date the activity is recorded in the document.

4. Document the explanation to substantiate the entry and the reason for the delay in recording.

5. Missing entry in the GMP records for non-retrieval data should be handled through event investigation procedure (For example, operator missed the reading of drying temperature during the operation, where there is no automatic data recording mechanism in place).

Working with blank or unused space

Blank/Unused space in the GMP records should be strikeout as below with single line with sign and date to ensure that record cannot be added at a later date.

Cancellation of GMP records

Cancellation of GMP records should only be allowed in the rare case with the approval of QA and in exceptional cases such as spillage of chemical on the record. Event investigation procedure should be followed to determine

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further course of action. The reason for cancellation should be documented for cancellation of the document and signed by area person-in-charge and QA.

CONCLUSION

This paper has presented an overview of the main types of documentation found within the pharmaceutical sectors. It has provided suggestions for good practice examples of how the documentation can be designed, produced, and controlled as part of a compliant GMP system. Good documentation practices are an essential part of GMP and compliance. When implemented, the recommendations presented in this paper will help with maintaining control and ensuring compliance in a GMP environment.

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