Gmp good documentation practices

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. Introduction The effective control and management of documentation is a critical part of the good manufacturing practice (GMP) program within the organization. The accurate capture of information plays an important part in the manufacture of pharmaceuticals and medical devices [1]. GMP is that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate for their intended use [2]. To comply with GMP, facilities require documented systems based on specifications, manufacturing and packaging instructions, procedures, and records. In particular, specific batch manufacturing documentation must be in place. These documents must make it possible to trace the history of each batch. This traceability needs to be possible for a minimum defined period that is typically one year after expiry of the batch. These types of records are essential for the quality assurance system. Documentation is also key to GMP compliance for it ensures traceability of all development, manufacturing, and testing activities. Documentation provides the route for auditors to assess the overall quality of operations within a company and the final product [3]. For example, with the FDA Code of Federal Regulations (CFR), 21CFR 211.180(e), records and reports, states: "written records…shall be maintained so that data therein can be used for evaluating…the quality standards of each drug product…". This extract thereby links the importance of good documentation to GMP. This paper presents an overview of good documentation practices applicable to those working in the pharmaceutical and healthcare sectors. Specific topics for discussion include the following: Good manufacturing practice and documentation including errors and error correction Document fundamentals Document creation Document management Types of documents Best practices for document creation, including style and layout Completing documents and record-keeping Electronic records Document storage Good Manufacturing Practice and Documentation There are a number of aspects of GMP that relate to documentation. GMP requires that documents should be: Controlled within the quality system Approved, signed and dated Regularly reviewed Retained, and Can be superseded within the quality system. Pharmaceutical and other healthcare organization must have "good" documentation practices. Whether the term "GDP' should be used to represent "good documentation practice" is contentious since GDP is more commonly used as an acronym for "good distribution practice"' in relation to the distribution of medicinal products. Types of Documentation Documentation refers to both printed forms and electronic systems. Broadly speaking, documentation types can be classified as: Specifications Manufacturing and packaging instructions Standard operating procedures Records. More specifically, the various types of documents found within a typical pharmaceutical organization include: Technical agreements Confidentiality agreements Technical reports Quality system related documents Quality Manual SOP's Validation protocols and reports Deviation reports Audit plans Validation Master Plans and validation documents including URS, DQ, FAT, IQ, OQ, PQ, and Validation reports Test material related documents including product specification, test material receipt, and reports Personnel related documents including training records Facility related documents including floor plans, HVAC plans, and environmental specifications Deviation forms including unplanned deviations and system failure investigation Change control Worksheets, notebooks, and logbooks Documentation must be clear, free from errors, subject to regular review, and be kept up-to-date. 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 Errors Common documentation errors that commonly appear in FDA warning letters and reports from other regulatory authorities include [4]: Documentation not contemporaneous Use of ditto marks Use of signature stamp Failure to use ink as specified by procedure 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 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. Document Fundamentals There are many different types of documents found within pharmaceutical organizations, each serving a different purpose [5]. 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 is illustrated in Figure 1. Figure 1: Classic Documentation Hierarchy The vast majority of documents are procedures or records. The most common examples of a procedure within the pharmaceutical organization are standard operating procedures (SOP) [6]. A record is often related to a specific SOP and carries the confirmatory details required of that SOP. For example, the SOP for a sterility test record should require details such as the product name, its batch number, and its test result. Document Creation The creation of documentation can be conceived very much like a process. In doing so, the first stage can be described as event capture. However, the information or event has no status unless it can be verified or approved, which is the second stage. The last part of the process is to communicate the event, in this context by circulating and implementing the document. To illustrate this consider a laboratory test common to many microbiology laboratories - the gram stain technique. To document the procedure, we need to write down the steps which capture the process. As part of a controlled system, the steps need to be verified as being correct and the procedure "signed of" (approval stage). The procedure can then be issued in into routine use along with associated training, which is the communication stage. Figure 2: Documentation Flow Path Document Management Each pharmaceutical organization should have a system for documentation management. This sets out the rules and mechanisms for creating and controlling a document. GMP makes certain requirements of a documentation system such as: Assigning responsibility to an individual for control of the system Ensuring layout, approval, authorization and unique identification of all documents is provided for often by a master documentation SOP Having a master documentation SOP to include: Procedures for issue, retrieval, re-issue, maintenance of currency and traceability Procedures for determining the need for documents Identification of documents to be included in batch dossiers (for batch release) Linkage of documents to licenses and regulatory requirements Outlining audit requirements for the documentation system Ensuring that only the most up to date version is ever used Retention times and archiving. 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: 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. Document approval Documents must be approved for use. They must be approved, signed, and dated by appropriate authorized personnel. 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. 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. 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. Types of Documents The different types of documents found within pharmaceutical and medical device facilities were described earlier. The main types of documents are now discussed in more detail with differences between the different types noted. Specifications Specifications are documents related to starting materials, packaging components, and finished products. They describe the standards to which these materials and products must comply if they are to be approved for use in manufacturing or for commercial sale. For example, the finished product specification should contain: The designated name of the product and the code reference where applicable The formula or suitable a reference A description of the pharmaceutical form and package details Directions for sampling and testing or a reference to procedures The qualitative and quantitative requirements with the acceptance limits. For example, the sterility test or absence of specified pathogens The storage conditions and any special handling precautions, where applicable Shelf-life. Instructions All instructions to personnel (for example, media manufacture, bacterial identification, analytical methods, and so on) should be clear, precise, unambiguous, and written in numbered steps. They should be written in a language and style that the user can readily understand. Associated with instructions are records. These can be either combined with the instruction or in a separate document. Batch Documentation A major element in final product release should be a review of all the relevant batch documentation to ensure the presence of all necessary information and the satisfactory completion of all necessary records. This will include sterilizer charts, microbiological testing certificates of analysis, process records, test results, and so on. Procedures and Records In addition to the instruction and associated records described above, specific procedures including material receipt, sampling, testing rejection, complaints, and other documents are also required. Depending of the type of document GMP expectations are that the document carries: Product name Description of the item Reference number and item code Pack or batch size List of materials Specific precautions or instructions Names of associated personnel Dates and times Version number Approvals. Best Practices for Document Creation and Use A company should continually evolve good practices for creation of documents. It is important that documents are designed, prepared, reviewed, and distributed with care. Documents also must be approved, signed, and dated by the appropriate competent and authorized persons. Further, documents must be regularly reviewed and kept up-to-date. When a document has been revised, systems must be operated to prevent inadvertent use of superseded documents. It is especially important that only current documentation should be available for use [7]. A further important consideration is to ensure that the records can be kept in an orderly fashion to facilitate retrieval at some unspecified time in the future. Best practices extend to the writing of the document. Using words that everyone can understand – minimizing jargon, acronyms, and abbreviations -- and using words with unambiguous meaning can help the reader to more easily understand and interpret the document. Key "readability" qualities for a document include [8]: Concise: Present information clearly so it can be easily understood with no room for misinterpretation. For example, the date format "06/05/14" can cause confusion. It is better to use one that is unambiguous, such as "05 jun 2014," especially if the document is used in the US and Europe. Legible: Information should be readable and leave no room for error. For example, hand-written data that are not legible may create errors in data analysis or result in missing data. Accurate: Documentation should be error-free—properly reviewed, verified and approved. Information should be recorded as an event happens and not after the fact to avoid recording "what you remember" rather than "what actually happened." Traceable: Documentation should be traceable. It should be made clear who logged the information, what it was, and when and why it was documented. To help with efficient location of records, attention should be paid to numbering including the version number for traceability. Simple sequential number of documents only works for a small number of documents. In most cases a defined structure to the numbering system is needed. For example, 001 - 100 could represent regulatory documents, 101 – 200 could represent QC testing documents, and 201 -300 could represent production documentation. This system may still limiting. The numbering system may need to include references to the site, a system (production, QC, validation, and so on) as well as its sequential number. Document Style and Layout It is often helpful to adopt a specific document style for consistency of operations. Elements of the style should be specified in an approved procedure. These might include [9] Logo Pagination/ layout to prevent confusion and ensure the document is kept in order Headers and footers Font including the size is useful to minimize errors introduced when changing between fonts Page numbers Executive summary Changes - Change control is important for traceability Circulation list - to ensure the document is reviewed and received by the appropriate personnel Table of contents Authorization levels stated on document Cross references Revision history Definitions Content (context and meaning) A clear area for recording problems/ incidents Use of pictures, flow charts, diagrams as suitable alternatives to text. Care should be taken in designing and stylizing documentation. Documents must have unambiguous contents. The title, nature, and purpose should be clearly stated. They must be laid out in an orderly fashion. Documents must be easy to check. Reproduced documents must be clear and legible. Many people do not consider the importance of how key information is presented within a document. This can result in the reader wasting time or not conducting the correct tasks. For example, a poorly structured document could ask the user to conduct a task that requires some action to be performed prior to the subject task – but only mentions the pre-work at the end of the document and with no reference to the pre-work at the beginning. Helpful considerations for layouts include the following: Cover page with identifiers and status Table of contents – creating a road map through the document Scope and applicability section Introduction Information and instructions in a logical sequence Additional information and detail. Numerical information must include the correct use of units. The use of color coding in graphical information, such as black lines for existing pipework and red lines for new pipework, might also be useful. The narrative must consider writing style, nomenclature, and dealing with errors and corrections. When considering the numerical issues, what are viewed as standard units? Think about mathematical symbols and the order in which calculations are performed. For example, the bodmas approach (b)rackets (o)rder (d)divide (m)ultiply (a)ddition (s)ubtraction, is useful. If someone gets the sequence wrong, they will get the wrong result. It is also important to think about the rules on rounding, i.e., Above 0.5, round up, etc. Finally, consider standardizing symbols in drawings. It is useful to consider different styles to accommodate the different reading styles of readers. There are thought to be three styles based on the linguistic, logical and spatial talents. These can be summarized as [10]: Linguistic talent. There is a strong ability to write and talk fluently. Phrases like "gift of the gab" often apply. Individuals in this category can also write and read well. Shakespeare had linguistic talent. Logical talent. There is strong ability to think logically and are quick in calculating odds and statistics. Albert Einstein had logic talent. Spatial talent. There is strong ability to image things in the "mind's eye." These people often have good navigational skills such as Christopher Columbus. The following should be considered whenever possible: Narrative – written text Tabular – tables Charts – bar charts, pie charts Color – bold – underlined text Pictures – photographs, images Diagrams – 2d, 3d Process logic – flowcharts Including various combinations of the above is extremely useful. A flow chart might help with navigating the document while pictures are very useful in dressing procedures for entry into cleanrooms. Tables are useful for summarizing data such as microbial limits for environmental monitoring. The use of cross referencing in documents is helpful in keeping the document short and manageable. Be careful of cross referencing too many documents as this can be self-defeating. The user will not follow the procedure if they have to locate too many other documents. Finally, consideration of the end user when writing is also extremely important. Too often documents are written by managers or technical staff without thought for the people that will be using them. Ideally it is recommended that the end user writes the document. Completing Documents and Record-Keeping After documents have been designed, prepared, and approved, they must be used and completed properly. For example, where documents require the entry of data, these entries must be made in clear legible handwriting using a suitable indelible medium -- not a pencil. Sufficient space must be provided for entries. With such entries, it is important that any correction made to a document or record must be signed or initialed and dated; the correction must permit the reading of the original information. Where appropriate, the reason for the correction must be recorded. With record-keeping in general, a record must be kept at the time each action is taken. All activities concerning the conduct of preclinical studies, clinical trials, and the manufacture and control of products must be traceable. Electronic Records The advent of computerized systems caused industry to move away from paper-based systems to paper-less systems. Electronic records offer many advantages. The reality is that typically there is a balance between the two. For example, consider a record for the absence of pathogen test on a non-sterile product. Recording the test result presents us with two options. Firstly it can and often is written on a log sheet. Secondly we can use a laboratory information management system (LIMS) to record the result electronically [11]. As a controlled form it will be created in Microsoft Word (electronic) and printed onto paper to check it so it can be signed for approval giving it status. This can be done on screen but many people prefer to review a hard copy. Approval can be electronic recording user name and password, or the printed document can be physically signed. In the latter case, the approved document could be scanned so it can be stored, distributed, and referenced electronically. A physically approved document will need photocopying if it is to be distributed in the "paper world." Electronic distribution of a physically signed document can save on paper but does present problems mainly from the scanning process. A scan that creates a picture of the original will be a very large file. Use of optical character recognition in the scanning process produces small files, but the scanning process introduces errors where characters may get missed or replaced requiring a further proof read often from a paper printout. During the active stage, personnel may prefer a hard copy to work from so that an electronic document will be printed onto paper. Archiving of paper records is costly in terms of space and to some degree retrievability, but little more in terms of maintenance. Archiving of electronic records presents more challenging problems. They only exist as a series of "1's" and "0's" (binary code) on storage media like a CD ROM. With electronic record archiving, the technology window must be understood. This means that the data might be available on the CD, but after 5 years there may not be any hardware that can read it. Essential to electronic record archiving is that companies have an adequate migration strategy. Paper records are still usable after several thousand years but data on discs may be lost after only 5-10 years, or a shorter period if the discs are not properly controlled. The migration strategy should also include the regular transfer of data onto fresh media, even if the hardware has not changed. The requirements for electronic records and signatures are dealt within the US title 21 part 11 of the Code of Federal Regulations (CFR). Although organizations do not have to use electronic records and signatures, if they do, they must comply with the CFR. It is important that such records are afforded the equivalence to paper records and hand written signatures. The CFR make it clear that procedures shall be followed, records should be documented at the time of performance, and deviations recorded and justified. Document Storage Storage of critical records must at secure place, with access limited to authorized persons. In relation to this, 21CFR 211.180(d) states "…these records or copies…shall be subject to photocopying or other means of reproduction as part of such inspection. Records that can be immediately retrieved from another location by computer or other electronic means shall be considered as meeting the requirements of this paragraph." The storage location must ensure adequate protection from loss, destruction, or falsification, and from damage due to fire, water, and other disasters. Records which are critical to regulatory compliance or to support essential business activities must be duplicated on paper, microfilm, or electronically, and stored in a separate, secure location in a separate building from the originals. Data may be recorded by electromagnetic or photographic means, but detailed procedures relating to whatever system is adopted must be available. Accuracy of the record should be checked as per the defined procedure. If documentation is handled by electronic data processing methods, only authorized persons should be able to enter or modify data in the computer, access must be restricted by passwords or other means, and entry of critical data must be independently verified. If electronic, photographic or other data processing systems are used for the retention of documents, an appropriate storage for required duration is necessary to protect against loss or damage. It is particularly important that during the period of retention, the data can be rendered retrievable and legible within an appropriate period of time. This means having a validated system of data recall. The data should also be available in a legible form. Rapid retrieval of reports and data is essential for audits. Summary This paper has presented an overview of the main types of documentation found within the pharmaceutical and medical device 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. References Hargreaves, P. (2007). "Good Manufacturing Practice in the Control of Contamination" in Deyner, S.P. and Baird, R.M. (eds.), Guide to Microbiological Control in Pharmaceuticals and Medical Devices, 2nd edition, CRC Press, Boca Raton, FL, pp121-142. Patel, K. T. and Chotai, N.P., (2008). Pharmaceutical GMP: Past, Present, and Future--a Review. Pharmazie.;63(4):251-5. Todd, J. I. (2007). Good Manufacturing Practice for Immunological Veterinary Medicinal Products. Rev Sci Tech.;26(1):135-45. Göbel, C., Baier, D., Ruhfus, B. and Hundt, F. (2009). 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