# Chapter 4: Documentation

**Reasons for changes:** The GMP/GDP Inspectors Working Group and the PIC/S Committee jointly recommended that the current version of Chapter 4, on documentation, is revised to reflect changes in regulatory and manufacturing environments. The revised guideline clarifies requirements and expectations from Regulatory Authorities with regards to documentation and takes into account related changes for Annex 11 of the GMP Guide.

**Document map**

## PRINCIPLE

4.1. Documentation constitutes an essential part of the quality assurance system and is key to operating in compliance with GMP requirements. The various types of documents and means used should be fully understood and defined in the regulated user's pharmaceutical quality system.

4.2. It should be determined by the regulated user which legal provisions apply to documentation considering new technologies, hybrid solutions and services used.

4.3. Appropriate documentation practices should be applied with respect to the type of document regardless of the applied technology or service used.

4.4. The present document was supplemented by requirements regarding new technologies, hybrid solutions and new services, whereby a risk-based approach as element of a data governance system is considered pivotal for scalability of integrity control measures.

4.5. Quality risk management principles should be applied to ensure that the pharmaceutical quality system includes sufficient instructional details. It should facilitate a common understanding of the requirements. In addition to providing for recording of the various processes and risk-based evaluation of any observations, it should demonstrate the ongoing application of all requirements.

4.6. Suitable controls should be implemented using a risk-based approach to ensure the accuracy, integrity, availability, and legibility of documents. Documents should be free from errors and available in human readable form.

4.7. Documentation may exist in a variety of forms, including paper-based, electronic, or other means (e.g. photography, imagery, video and audio recordings). The main objective of the documentation system is to establish, control, monitor and record all activities which directly or indirectly impact on all aspects of the quality and safety of medicinal products, using a risk-based approach.

4.8. Whether documents are created, stored, and managed electronically, paper based, by other means or through a hybrid system, they must meet the same GMP requirements for legibility, accuracy, integrity, and completeness throughout the whole lifecycle. This also applies when documentation is outsourced.

4.9. There are two primary types of documentation used to manage and demonstrate GMP compliance:

i. instructions (directions, requirements) and
ii. records/reports.

## DATA GOVERNANCE SYSTEMS

4.10. Regardless of how documents are created, handled, stored, and managed (i.e., using electronic, paper-based, or hybrid systems), the regulated user should establish a data governance system integral to the pharmaceutical quality system to define, prioritise and communicate their data integrity risk management activities. Arrangements for data governance should be documented and reviewed regularly.

4.11. Regulated users should design and operate a data governance system which provides an acceptable state of control based on the risk assessment, which is documented with supporting rationale. A data governance system should be consistent with the principles of quality risk management.

4.12. To ensure integrity of data the governance system should cover the entire data lifecycle and ensure controls commensurate with the principle of quality risk management. The data lifecycle should refer to:

i. Creation and recording of data.
ii. Processing of (raw) data to reported (derived) data.

iii. Verification of completeness, consistency and accuracy of all data (raw and derived data). For derived data the traceability which allows reconstruction of all data processing activities should be maintained.
iv. Decision making relying on data (or derived data).
v. Retaining, archiving and retrieval of data. To protect it from loss or unauthorised alteration it should be commensurate with the principles of quality risk management.
vi. Retirement or destruction of data at the end of the lifecycle in a controlled manner.

4.13. Data governance systems should rely on a risk management approach and consider:
i. Data criticality (impact to decision making and product quality) and
ii. Data risk (opportunity for data alteration and deletion, and likelihood of detection / visibility of changes by the regulated user's routine review processes).

4.14. Data governance systems should rely on the incorporation of suitably designed systems, the use of technologies and data security measures, combined with specific expertise to ensure that data integrity is effectively controlled over the data lifecycle.

4.15. Data governance systems should address data ownership throughout the entire lifecycle.

4.16. Data governance systems should consider the design, operation and monitoring of processes and systems to comply with the principles of data integrity.

4.17. Data governance systems should consider risk mitigation. The effectiveness of risk mitigation measures should be reviewed regularly, regardless of whether they are temporary or permanent. Residual risks should be reviewed periodically and communicated to management.

4.18. Data governance systems should consider and ensure the periodic review of service provider's data management policies and risk control strategies intended to minimise potential risks to data integrity. The frequency of such reviews should be based on the criticality of the services provided, using risk management principles.

## RISK MANAGEMENT

4.19. The regulated user should adopt a risk-based approach in documentation throughout the entire lifecycle of data, regardless of the technology, hybrid solution or service used and should demonstrate an understanding for data criticality, data risk and data quality.

4.20. Controls over the data lifecycle should be established which are commensurate with the principles of quality risk management. The depth of data governance and risk management activities should be justified and commensurate with the risks to product quality and patient safety.

4.21. Decisions on the extent of measures to ensure data integrity should be based on a documented rationale and documented risk assessment taking into consideration data criticality and data risk.

4.22. Irrespective of processes used to generate electronic data, they must be included in the requirements for the qualification or validation of the relevant computerised systems according to Annex 11.

## GENERAL REQUIREMENTS FOR DOCUMENTATION

4.23. The pharmaceutical quality system should describe all documents required to ensure product quality and patient safety. Documents may be created, recorded, provided, approved, communicated, stored, and archived electronically, paper based or in a hybrid system. The reliance on electronic, paper-based or different means, hybrid solutions or hosted services in maintenance and retention of documentation requires the compliance with all EU GMP provisions including Annex 11 if decision making in manufacturing (e.g. batch release based on in-process controls and process analytical technologies) is supported by automatic validation scripts or artificial intelligence (Annex 22).

4.24. The accountability for the integrity of documents, records or (raw) data produced or processed

with artificial intelligence or any other automatic means (e.g. validation scripts) rests with the regulated user.

4.25. The support by any automatic means (e.g. validation scripts or artificial intelligence) should be included in a pharmaceutical quality system regardless of the service located on premise or as a hosted service. The records created electronically should enable a trend analysis of quality-critical data.

4.26. To ensure data integrity, data which is recorded or processed electronically should not be converted to or stored in a paper form unless it meets the requirements set out in section 13 "hybrid systems" or the conversion is validated or verified for accuracy.

## MASTER DOCUMENTS

4.27. Specifically required master documents (not exhaustive list):

i. **Site Master File**: Refer to EU GMP Guidelines, Volume 4 "Explanatory Notes on the preparation of a Site Master File".

ii. **Validation Master Plan**: A document describing the key elements of the site qualification and validation program. Master documents should be evaluated and reviewed on a regular basis.

iii. **Instructions** (directions, or requirements) type:

- **Specification:** Refer to glossary for definition
- **Manufacturing Formulae, Processing, Packaging and Testing Instruction:** Provide complete detail on all the starting materials, equipment, and computerised systems (if any) to be used and specify all processing, packaging, sampling, and testing instructions to ensure batch to batch consistency. In-process controls and process analytical technologies to be employed should be specified where relevant, together with acceptance criteria.
- **Procedures:** (Otherwise known as Standard Operating Procedures, or SOPs), documented set of instructions for performing and recording operations.
- **Protocol:** defined set of activities to provide instructions for performing and recording certain discreet operations.
- **Technical / Quality Agreement:** Written proof of agreement between contract givers and acceptors for outsourced activities.

**iv. Record/Report type:**

- **Record:** Provide evidence of various actions taken to demonstrate compliance with instructions, e.g. activities, events, investigations, and in the case of manufactured batches a history of each batch of product, including its distribution. Records include the raw data which is used to generate other records. For electronic records regulated users should define which data are to be used as raw data. At least, all data on which quality decisions are based should be defined as raw data.

  Records can also exist as hybrid records which is a combination of paper records, electronic records or by other means. The completeness and integrity of records, including all relevant raw data and meta data should be ensured and protected based on risk.

- **Certificate of Analysis:** Provide a summary of testing results on samples of products or materials[1] together with the evaluation for compliance to a stated specification.

[1] Alternatively, the certification may be based, in-whole or in-part, on the assessment of real time data (summaries and exception reports) from batch related process analytical technology (PAT), parameters or metrics as per the approved marketing authorisation dossier.

- **Report:** Document the conduct of exercises, studies, assessments, projects or investigations, together with results, conclusions and recommendations.

**Specifications**

4.28. There should be approved and updated specifications for starting and packaging materials, intermediate, bulk, finished products, process aids and other quality critical material, as applicable. Specifications should include all attributes which are relevant for product quality on each stage of material or manufacture.

**Specifications for starting and packaging materials**

4.29. Specifications for starting and primary or printed packaging materials should include the product and its reference code, if applicable:

i. A description of the materials, including:
   - The designated name and the internal code reference.
   - The reference, if any, to a pharmacopeial monograph.
   - The approved suppliers and, if applicable, the original producer of the material.
   - A specimen of printed materials.

ii. Directions for sampling and testing.

iii. Qualitative and quantitative requirements with acceptance limits.

iv. Storage conditions and precautions.

v. The maximum period of storage before re-examination.

**Specifications for intermediate and bulk products**

4.30. Specifications for intermediate and bulk products should be available for critical steps or if these are purchased or dispatched. The specifications should be similar to specifications for starting materials or for finished products, as appropriate.

**Specifications for finished products**

4.31. Specifications for finished products should include or provide reference to:

vi. The designated name of the product and the code reference where applicable.

vii. The formula.

viii. A description of the pharmaceutical form and package details.

ix. Directions for sampling and testing.

x. The qualitative and quantitative requirements, with the acceptance limits.

xi. The storage conditions and any special handling precautions, where applicable.

xii. The shelf-life.

**Manufacturing Formula and Processing Instructions**

4.32. Approved, written Manufacturing Formula and Processing Instructions should exist for each product and batch size to be manufactured.

4.33. The Manufacturing Formula should include:

i. The name of the product, with a product reference code relating to its specification.

ii. A description of the pharmaceutical form, strength of the product and batch size.

iii. A list of all starting materials to be used, with the amount of each, described;

mention should be made of any substance that may disappear while processing, of processing aids needed or any other material relevant for product quality.

iv. A statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable.

4.34. The Processing Instructions should include:

i. A statement of the processing location and the principal equipment to be used.

ii. The methods, or reference to the methods, to be used for preparing the critical equipment (e.g. cleaning, assembling, calibrating, sterilising).

iii. Checks that the equipment and workstation are clear of previous products, documents or materials not required for the planned process, and that equipment is clean and suitable for use.

iv. Detailed stepwise processing instructions [e.g. checks on materials, pre-treatments, sequence for adding materials, critical process parameters (time, temp etc)].

v. The instructions for any in-process controls with their limits.

vi. Where necessary, the requirements for bulk storage of the products; including the container, labelling and special storage conditions where applicable.

vii. Any special precautions to be observed.

**Packaging Instructions**

4.35. Approved Packaging Instructions for each product, pack size and type should exist. These should include, or have a reference to, the following:

i. Name of the product; including the batch number of bulk and finished product.

ii. Description of its pharmaceutical form, and strength where applicable.

iii. The pack size expressed in terms of the number, weight or volume of the product in the final container.

iv. A complete list of all the packaging materials required, including quantities, sizes and types, with the code or reference number relating to the specifications of each packaging material.

v. Where appropriate, an example or reproduction of the relevant printed packaging materials, and specimens indicating where to apply batch number references, and shelf life of the product.

vi. Checks that the equipment and workstation are clear of previous products, documents or materials not required for the planned packaging operations (line clearance), and that equipment is clean and suitable for use.

vii. Checks on functioning of any electronic code readers, label counters or similar devices.

viii. Special precautions to be observed, including a careful examination of the area and equipment in order to ascertain the line clearance before operations begin.

ix. A description of the packaging operation, including any significant subsidiary operations, and equipment to be used.

x. Details of in-process controls with instructions for sampling and acceptance limits.

**Batch Processing Record**

4.36. A Batch Processing Record should be kept for each batch processed. It should be based on

the relevant parts of the currently approved Manufacturing Formula and Processing Instructions, and should contain the following information:

i. The name and batch number of the product.

ii. Dates and times of commencement, of significant intermediate stages and of completion of production.

iii. Identification (initials) of the operator(s) who performed each significant step of the process and, where appropriate, identification (initials) of the person who checked these operations.

iv. The batch number and/or analytical control number as well as the quantities of each starting material weighed (including the batch number and amount of any recovered or reprocessed material added).

v. Any relevant processing operation or event and major equipment used.

vi. A record of the in-process controls and the initials of the person(s) carrying them out, and the results obtained.

vii. The product yield obtained at different and pertinent stages of manufacture.

viii. Notes on special problems including details, with signed authorisation for any deviation from the Manufacturing Formula and Processing Instructions.

ix. Approval by the person responsible for the processing operations.

**Note:** Where a validated process is continuously monitored and controlled, then automatically generated reports may be limited to compliance summaries and exception/ out-of-specification (OOS) data reports.

With regards to decision making in manufacturing supported by automatic validation scripts or artificial intelligence refer to paragraph 4 of this document.

**Batch Packaging Record**

4.37. A Batch Packaging Record should be kept for each batch or part batch processed. It should be based on the relevant parts of the Packaging Instructions.

4.38. The batch packaging record should contain the following information:

i. The name and batch number of the product.

ii. The date(s) and times of the packaging operations.

iii. Identification (initials) of the operator(s) who performed each significant step of the process and, where appropriate, the name of any person who checked these operations.

iv. Records of checks for identity and conformity with the packaging instructions, including the results of in-process controls.

v. Records of checks that the equipment and workstation are clear of previous products, documents or materials not required for the planned packaging operations (line clearance), that equipment is clean and suitable for use, and that any electronic code readers, label counters or similar devices are functioning as expected.

vi. Details of the packaging operations carried out, including references to equipment and the packaging lines used.

vii. Whenever possible, samples of printed packaging materials used, including specimens of the batch coding, expiry dating and any additional overprinting.

viii. Notes on any special problems or unusual events including details, with signed

authorisation for any deviation from the Packaging Instructions.

ix. The quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed or returned to stock and the quantities of obtained product, to provide for an adequate reconciliation. Where there are validated electronic controls in place during packaging there may be justification for not including this information

x. Approval by the person responsible for the packaging operations.

**Receipt**

4.39. There should be written procedures and records for the receipt of each delivery of each starting material, (including bulk, intermediate or finished goods), primary, secondary and printed packaging materials and QC-samples. The records of the receipts should include:

i. The name of the material on the delivery notes and the containers.

ii. The "in-house" name and/or code of material (if different from a).

iii. Date of receipt.

iv. Supplier's name and, manufacturer's name.

v. Manufacturer's batch or reference number.

vi. Total quantity and number of containers received.

vii. The batch number assigned after receipt.

viii. Any relevant comment.

ix. If applicable, proof of verification that temperature during transportation were within the approved limit.

4.40. There should be written procedures for the internal labelling, quarantine and storage of starting materials, packaging materials, QC samples and other materials, as appropriate.

**Sampling**

4.41. There should be written procedures for sampling, which include the methods and equipment to be used, the amounts to be taken and any precautions to be observed to avoid contamination of the material or any deterioration in its quality (reference to EU GMP Guideline Volume 4, Chapter 6 "Quality Control").

**Testing**

4.42. There should be written procedures for testing materials and products at different stages of manufacture, describing the methods and equipment to be used. The tests performed should be recorded (reference to EU GMP Guideline Volume 4, Chapter 6 "Quality Control").

**Other**

4.43. Written release and rejection procedures should be available for materials and products, and in particular for the certification for sale of the finished product by the Qualified Person(s). All records should be available to the Qualified Person at the time of the release decision. A system should be in place to indicate special observations and any changes to critical data.

4.44. Records should be maintained for the distribution of each batch of a product in order to facilitate recall of any batch, if necessary.

4.45. There should be written policies, procedures, protocols, reports and the associated records of actions taken, or conclusions reached, where appropriate, for GMP relevant actions, including

but not limited to the following examples:

i. Validation and qualification of processes, equipment and systems.
ii. Equipment assembly and calibration.
iii. Data integrity.
iv. Technology transfer.
v. Maintenance, cleaning and sanitation.
vi. Personnel matters including signature lists, training in GMP and technical matters, clothing and hygiene and verification of the effectiveness of training.
vii. Environmental monitoring.
viii. Pest control.
ix. Complaints.
x. Recalls.
xi. Returns.
xii. Change control.
xiii. Investigations into deviations.
xiv. non-conformances e.g. out of specifications.
xv. Internal quality/GMP compliance audits.
xvi. Summaries of records where appropriate (e.g. product quality review).
xvii. Supplier audits.

4.46. Clear operating procedures should be available for major items of manufacturing and test equipment.

4.47. Logbooks should be kept for major or critical analytical testing, production equipment, and areas where product has been processed or handled. They should be used to record in chronological order, as appropriate, any use of the area, equipment/method, calibrations, maintenance, cleaning or repair operations, including the dates and identity of people who carried these operations out.

4.48. An inventory of documents within the pharmaceutical quality system should be maintained.

**GENERATION AND CONTROL OF DOCUMENTATION**

4.49. All types of documents (instructions and/or records) should be defined and adhered to regardless of the documentation technology, hybrid solution or service. The technology, hybrid solution or provided service needs to be understood regardless of complexity, should be adequately documented, and validated with risk-based controls in place. Relationships and control measures for master documents, official copies, data handling and records need to be defined for both hybrid and homogenous systems regardless of the type of service. Appropriate controls for documents should be implemented to ensure the completeness, integrity and legibility of the records throughout the lifecycle.

4.50. Documents should be designed, prepared, reviewed, and distributed in a controlled manner. They should comply with the relevant parts of Product Specification Files, Manufacturing and Marketing Authorisation dossiers, or dossiers of Investigational Medicinal Products, as appropriate. The reproduction of working documents from master documents should not allow any error or alteration to be introduced through

the reproduction process.

4.51. Documents should be regularly reviewed and kept up to date. Documents should be approved, signed, and dated by appropriate and authorised personnel. Documents should have unambiguous contents and be uniquely identifiable. The effective date should be defined.

4.52. Documents containing instructions should be laid out in an orderly fashion and be easy to review. The style and language of documents should fit with their intended use. Standard operating procedures, work instructions and methods should be written in an imperative mandatory style by using predefined format. Data entry formats for completion of documents should be clearly defined. Written instructions may be supported with pictures, photos or videos. The documents containing the instructions should be easily accessible at the place where the described activities are carried out.

4.53. Instructions and procedures within the Quality Management System should be regularly reviewed and kept updated.

4.54. The issuance, revision, superseding and withdrawal of all documents should be controlled with maintenance of revision histories.

4.55. Hand-written instructions are discouraged. Where documents require the manual entry of data, sufficient space should be provided for such entries to ensure adequately clear and legible manual recording.

**GOOD DOCUMENTATION PRACTICE**

4.56. Good Documentation practices are key to ensuring data integrity, and a fundamental part of a well-designed pharmaceutical quality system.

4.57. Procedures outlining good documentation practices and arrangements for document control should be available within the pharmaceutical quality system. Good documentation practices should be implemented and enforced to ensure data integrity.

4.58. Data entries should be accurate, and made in clear, legible, indelible way. Recorded media should be durable throughout the retention period. If this is not feasible, then true copies should be generated. For this case a documented system should be in place to verify and record the integrity of the copy.

4.59. Records should be made or completed at the time each action is taken and in such a way that all GMP activities are traceable. It should be possible to identify the individual or the system that performed the task and when the task was performed.

4.60. Any alteration made to the entry on a document should be signed by the individual who made the change and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.

4.61. Records need to be a truthful and consistent representation of facts to ensure the accuracy of information, including data that is used to make critical decisions about the quality of products.

4.62. Specific controls should be implemented to ensure the integrity of raw data and results recorded on paper. These may include, but are not limited to:

i. control over the issuance and use of loose paper sheets (blank forms) at the time of recording data.

ii. control over the issuance of bound, paginated notebooks.

iii. control over the issuance and reconciliation of sequentially numbered copies of

397 blank forms with authenticity controls.

398 iv. Control that raw data is contemporaneously and accurately recorded by permanent
399 means.

400 4.63. Basic data integrity principles (table 1) applicable to both paper and electronic systems
401 (i.e. ALCOA ++):
402
403 **Table 1: Data integrity principles**

| Attributes | Requirement |
|---|---|
| Attributable | It should be possible to identify the individual or computerised system that performed a recorded task and when the task was performed. This also applies to any changes made to records, such as corrections, deletions, and changes where it is important to know who made a change, when, and why. |
| Legible | All records should be legible – the information should be readable and unambiguous in order to be understandable and of use. This applies to all information that would be required to be considered complete, including all original records or entries. Where the 'dynamic' nature of electronic data (the ability to search, query, trend, etc.) is important to the content and meaning of the record, the ability to interact with the data using a suitable application is important to the 'availability' of the record. |
| Contemporaneous | The evidence of actions, events or decisions should be recorded as they take place. This documentation should serve as an accurate attestation of what was done, or what was decided and why, i.e. what influenced the decision at that time. |
| Original | The original record can be described as the first capture of information, whether recorded on paper (static) or electronically (usually dynamic, depending on the complexity of the system). Information that is originally captured in a dynamic state should remain available in that state. |
| Accurate | Records need to be a truthful representation of facts to be accurate.<br>Ensuring records are accurate is achieved through many elements of a robust pharmaceutical quality system.<br>This can be comprised of:<br>• equipment related factors such as qualification, calibration, maintenance, and computer validation.<br>• policies and procedures to control actions and behaviours, including data review procedures to verify adherence to procedural requirements. |

| | |
|---|---|
| | • deviation management including root cause analysis, impact assessments and CAPA.<br>• trained and qualified personnel who understand the importance of following established procedures and documenting their actions and decisions.<br>Together, these elements aim to ensure the accuracy of information, including scientific data that is used to make critical decisions about the quality of products. |
| Complete | All information that would be critical to recreating an event is important when trying to understand the event. It is important that information is not lost or deleted. The level of detail required for an information set to be considered complete would depend on the criticality of the information. A complete record of data generated electronically includes relevant metadata. |
| Consistent | Information should be created, processed, and stored in a logical manner that has a defined consistency. This includes policies or procedures that help control or standardize data (e.g. chronological sequencing, date formats, units of measurement, approaches to rounding, significant digits, etc.). |
| Enduring | Records should be kept in a manner such that they exist for the entire period during which they might be needed. This means they need to remain intact and accessible as an indelible/durable record throughout the record retention period. |
| Available | Records should be available for review at any time during the required retention period, accessible in a readable format to all applicable personnel who are responsible for their review whether for routine release decisions, investigations, trending, annual reports, audits or inspections. |
| Traceable | Traceability is the ability to trace the history, modification or location of data by means of recorded identifications. |

## SIGNATURES IN GMP RELEVANT DOCUMENTATION

4.64. Signatures are essential for ensuring accountability for activities in a GMP environment at the time points the signatures are executed.

4.65. A signature represents the legally binding will of the signatory. The signatory should sign with date and time. If signatures by initials are in use a procedure defining abbreviated signatures should be in place.

4.66. The identification of the signatory should be possible. Data or documents which are associated with the signature should be clearly identified. The meaning of the signature (such as review, approval, responsibility, or authorship) associated with the signature should be clear.

4.67. The regulated user should establish a signature policy to ensure the adequate application of signatures. Personnel authorised to sign should be clearly identified by name and bound by name to the signature policy.

4.68. The regulated user should have identified those records which require a legally binding signature.

4.69. Signatures should be indisputable and traceable to the signatory and the signed document or record, regardless, if a signature is applied on paper or electronically.

4.70. If records exist electronically such records should be signed electronically. The use of a hybrid system should be avoided. If signatures exist parallel in paper and electronically (e.g. in hybrid systems), the regulatory relevant signature should be defined by the regulated user.

4.71. The signatory should be qualified and authorised to perform the relevant tasks or reviews.

4.72. The regulated user should define the signatory's role and responsibility in the signation process.

4.73. The regulated user should ensure that the signatory's role and qualification is consistent with the meaning (intent) of a signature.

4.74. To ensure the integrity of signatures during the whole life cycle of data the regulated user should establish the management and control of signatures as an element of a data governance system.

4.75. The data or documents which the signature is relevant for should fulfil the ALCOA++ principles.

**RETENTION OF DOCUMENTS**

4.76. It should be clearly defined which record is related to each activity and where this record is located, regardless of the technology, hybrid solution or service used. Risk-based control methods should be in place to ensure the integrity of the record throughout the lifecycle. The control measures should be covered by the validation scope. In case of electronic recording such measures should include back-up, restore and archiving procedures as well as physical and logical controls. If the regulated user relies on hosted services, it is the responsibility of the regulated user to understand, approve and justify the control measures of the hosted service provider based on a service level agreement. Records should be available for review at any time during the required retention period, accessible in a human readable format to all applicable personnel.

4.77. Specific requirements apply to batch documentation which must be kept for one year after expiry of the batch to which it relates or at least five years after certification of the batch by the Qualified Person, whichever is the longer. For investigational medicinal products, the batch documentation must be kept for at least five years after the completion or formal discontinuation of the last clinical trial in which the batch was used. Other requirements for retention of documentation may be described in legislation in relation to specific types of products (e.g. Advanced Therapy Medicinal

Products and products derived from human blood or human plasma) and specify that longer retention periods be applied to certain documents.

4.78. 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 Authorisation should be retained whilst the authorization remains in force. 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. Justification for this should be documented and should consider the requirements for retention of batch documentation; for example, in the case of process validation data, the accompanying raw data should 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.

4.79. A documented process for the disposal of records should be in place to ensure that the correct original records or true copies are disposed only after the defined retention period. Measures should be in place to reduce the risk of deleting the wrong documents. The access rights allowing disposal of records should be controlled.

**DATA INTEGRITY IN DOCUMENTATION**

4.80. The method of documentation should be integrated in the regulated user's pharmaceutical quality system. Documents or records should be controlled in a risk-based approach regardless of whether located in-house or in the form of hosted services. The regulated user should apply the principles of data integrity, data criticality and data risk within a data governance system and should consider the complete lifecycle of data. The data governance system should be an element of the pharmaceutical quality system. The ownership of data and the responsibility for data integrity should be defined.

4.81. Risk based control measures should be commensurate with the type and the complexity of a system. The pharmaceutical quality system should interface with independent review practices to detect risks to data integrity. Risks from human factors should be considered for effectively ensuring data integrity Risk-reducing measures such as second person oversight, verification and checks should be implemented where appropriate and in the appropriate time to ensure critical process and testing steps are accurately and contemporaneously recorded.

**HYBRID SYSTEMS**

4.82. They should be clearly defined and identified, and each contributing element of the system validated and controlled according to risk management principles.

4.83. A detailed description of the entire system should be available. The description should outline all major components, their functions, and interactions with each other as well as control for data management and data integrity. Procedures and records should be available to manage and appropriately control the interface between manual and computerised systems.

4.84. Appropriate quality risk management principles should be followed when assessing, defining, and demonstrating the effectiveness of control measures applied to the system.

4.85. Procedures should be in place to manage the review of data generated by hybrid

systems which clearly outline the process for the evaluation, approval and archiving of electronic and paper-based data.

## GLOSSARY

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| ALCOA++ | An acronym for "attributable, legible, contemporaneous, original and accurate", which puts additional emphasis on the attributes complete, consistent, enduring, available and traceable – implicit basic ALCOA principles. |
| Archiving | Long term, or permanent retention of completed documentation and relevant metadata in its final form for the purposes of reconstruction of a process or activity. |
| Automated script | A piece of code used to automate repetitive processes |
| Data | The contents of the record. Data may be defined as measurable or descriptive attribute of a physical entity, process, or event. |
| Data governance | The total sum of arrangements to ensure that data, irrespective of the format in which it is generated, recorded, processed, retained and used, will be attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring, and available throughout the data lifecycle. |
| Data integrity | Data integrity refers to the completeness, consistency, and accuracy of data. Complete, consistent, and accurate data should be attributable, legible, contemporaneously recorded, original or a true copy, accurate and traceable (ALCOA++). |
| Data lifecycle | All processes related to the creating, recording, processing, reviewing, changing, analysing, reporting, transferring, storing, migrating, archiving, retrieving, and deleting of data. |
| Data management | The set of all methodological, conceptual, organisational and technical measures and procedures for handling data with the aim of incorporating it into business processes. |
| Data risk | The combination of the probability of occurrence of harm and the severity of that harm related to data (incompleteness, alterations or loss which compromise the integrity of data). |
| Data criticality | The degree of influence that data have on product safety as well as the regulatory compliance of processes, decisions and product quality. |
| Data Risk Management | An activity to be applied throughout the lifecycle of data considering the need to ensure data integrity. Risk management consists of risk identification, risk assessment, risk mitigation and risk control. Risk management should link to other relevant procedures (e.g. configuration and change management, management processes for data, business risks, etc.). |
| Data Risk Assessment | The process of evaluating the risks associated with the regulated user's data. It ensures an efficient and effective approach to data integrity by considering the vulnerability of data to involuntary or deliberate alteration resulting in risk-based control measures. |

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| Data ownership | The allocation of responsibilities for control of data to a specific process owner. Companies should implement systems to ensure that responsibilities for systems and their data are appropriately allocated, and responsibilities undertaken. |
| Data quality | The degree to which a set of inherent characteristics (quality dimensions) of data fulfils requirements.<br>Data should be fit for use in their intended operational, decision-making, and other roles and should exhibit conformance to regulatory standards that have been set, so that fitness for use is achieved. |
| Document | A formatted compilation of data. Operations and activities that are memorialized in (electronic) records may consist of one or more documents that describe the activity in a moment of time. |
| Electronic record | Any combination of text, graphics, data, audio, pictorial, or other information representation in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system. |
| Hybrid system | A combination of paper based and electronic means. |
| Homogenous systems | A system that is either paper or electronically based on-premises or a cloud service. |
| Meta data | Describe the attributes of data and provides context and meaning. Metadata is any information used for the identification, description, and relationships of electronic records or their elements. Metadata gives data meaning, provides context, defines structure, and enables retrievability across systems, and usability, authenticity, and auditability across time. |
| Raw Data | Raw data is defined as the original record (data) which can be described as the first capture of stored information, whether recorded on paper or electronically. Information that is originally captured in a dynamic state should remain available in that state. |
| Record | Memorializes, or makes information permanent about, an action, activity and event that caused its creation. |
| Regulated user | Marketing Authorisation Holder, Manufacturers, control laboratories, importers, and wholesale distributors (if the wholesale distributor holds a manufacturing license). |
| Risk based approach for data integrity | A process to define critical data, documents and the actions used to monitor activities like capturing, derivation, migration, storage, communication and archiving to ensure that data and documents remain in a state of control throughout the entire lifecycle and to maintain its integrity. |
| Specification | A list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the test described. It establishes the set of criteria to which a material should conform to be considered acceptable for its intended use. “Conformance to specification” means that the material, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. |

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| True copy | An exact copy of original documentation that preserves the same content, meaning and attributes of the original. The term “true copy” is synonymous with “certified” or “verified copy”. |
| Type of service | On-premises IT service or outsourced hosted (cloud) IT service |
| Verified copy | Refer to definition of true copy |
| Data Risk Assessment | The process of evaluating the risks associated with the regulated user’s data. |