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1. Documentation and record management
2. Compliance monitoring and system performance

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Requirements for record management in pharmacovigilance

- Manufacturer must
  - record **all PV information**
  - ensure its handling and storage for **accurate reporting, interpretation and verification**
  - Put in place a **record management system** for all documents used for PV activities
    - retrievable and traceable with respect to timelines of investigations and decisions

- **Record management system** should support:
  - management of the quality of PV data
  - timely access to all records
  - effective internal and external communication
  - retention of documents in accordance with the applicable retention periods

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ALCOA

"Medicines regulatory systems worldwide have always **depended upon the knowledge of organizations** that develop, manufacture and package, test, distribute and monitor pharmaceutical products.

Implicit in the assessment and review process is **trust between the regulator and the regulated** that the information submitted in dossiers and used in day-to-day decision making is comprehensive, complete and reliable.

The data on which these decisions are based should therefore be complete as well as being **attributable**, **legible**, **contemporaneous**, **original** and **accurate**, commonly referred to as "ALCOA"

More on ALCOA later…

WHO Technical Report Series No. 996, 2016 (Annexure 5) Guidance on good data and record management practices

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Inspection observations with regards to documentation are increasing!

Reasons:

- Failures by organizations to:
  - apply robust systems that inhibit data risks
  - improve detection of situations where data reliability may be compromised
  - investigate and address root causes when failures do arise.

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Principles of good data and record management practices (GDRP)

1. Systematic approach should be implemented to provide a high level of assurance throughout the product life cycle
2. Applicability to both paper and electronic data
3. Applicability to contract givers and contract acceptors. Contract givers are ultimately responsible
4. Good documentation practices (GDocP) should be followed to ensure all records allow full reconstruction and traceability
5. Senior management ensure appropriate data management governance programs are in place:
    i. Application of modern QRM principles and good data management principles
    ii. Application of appropriate quality metrics
    iii. Assurance that personnel are not subject to commercial, political, financial and other organizational pressures or incentives
    iv. Allocation of adequate human and technical resources
    v. Ensure staff are aware of the importance of their role in ensuring data integrity

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Principles of good data and record management practices (GDRP) (contd.)

6. Quality culture.
    - Establish and maintain a working environment that minimizes the risk of non-compliant records and erroneous records and data
    - Transparent and open reporting of deviations, errors, omissions and aberrant results at all levels of the organization, irrespective of hierarchy
7. Quality risk management and sound scientific principles.
    - Robust decision making based on sound scientific and statistical principles, in turn based upon reliable data
8. Data life cycle management.
    - Management of data integrity risks throughout all phases of the process by which data are created, recorded, processed, transmitted, reviewed, reported, archived and retrieved
    - Should be subject to regular review

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Principles of good data and record management practices (GDRP) (contd.)

9. Record-keeping methodologies and systems, whether paper or electronic, should be designed in a way that encourages compliance with the principles of data integrity.

   ❑ Examples include, but are not restricted to:

   ✓ restricting ability to change any clock used for recording timed events

   ✓ Use of controlled forms for recording PV data accessible at all locations where activity is taking place (e.g., AEFI Form, telephonic record form)

   ✓ restricting user access rights to automated systems to prevent data amendments

   ✓ ensuring proximity of printers to sites of relevant activities

   ✓ ensuring access to original electronic data for staff performing data checking activities.

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Principles of good data and record management practices (GDRP) (contd.)

10. Data and record media should be durable.

    - For paper records, the ink should be indelible.
    - Temperature-sensitive or photosensitive inks and other erasable inks should not be used.
    - Paper should also not be temperature-sensitive, photosensitive or easily oxidizable.

11. Maintenance of record-keeping systems.

    - Implemented and maintained for both paper and electronic record-keeping based on scientific and technical progress.
    - Should be periodically reviewed for effectiveness and updated as necessary

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Quality risk management to ensure good data management

- Organizations should establish, implement and maintain an appropriate quality management system
  - elements documented in their prescribed format, e.g. quality manual
  - include a **quality policy statement** of management's commitment to an effective quality management system and to good professional practice
  - include **a code of ethics and code of proper conduct** to assure the reliability and completeness of data.
- Organization should establish:
  - ✓ appropriate infrastructure,
  - ✓ organizational structure,
  - ✓ written policies and procedures,
  - ✓ processes and systems that minimize situations impacting data integrity

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Role of Management

Management

- Must set realistic and achievable expectations for the true and current capabilities
- Monitor the processes
- Allocate necessary resources and enhance infrastructure, as required. Examples:
  - adequate design and maintenance of buildings, facilities, equipment and systems;
  - adequate reliable power and water supplies;
  - necessary training for personnel;
  - allocate necessary resources to the oversight of contract sites and suppliers
- Adopt a quality culture within the company that encourages personnel to be transparent about failures
- Map data processes and apply sound scientific principles throughout the data life cycle
- Make staff aware of the relevance of data integrity and importance of their role in protecting the safety of patients and the reputation of their organization
- Management reviews and regular reporting of quality metrics
- QPPV should have direct access to the highest level of management and directly communicate risks, so that senior management is made aware

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Contracted organizations, suppliers and service providers

- Responsibilities of both parties should comprehensively address the processes that should be followed to ensure data integrity
- Organization that outsources work has the responsibility for the integrity of all results reported
- Contract givers should therefore perform risk-based, due diligence
- When outsourcing databases and software provision, the contract giver should ensure that service provider is appropriately qualified and trained in GDRP (good data and record management practices).
- Their activities should be monitored on a regular basis
- Outsourcing organizations should verify the adequacy of the governance systems of the service provider
- Understand ownership and retrieval where data and document retention is contracted to third party:
  - physical location where the data are held, and the impact of local laws should also be considered.
  - Agreements contain consequences if the service provider denies, refuses or limits access to records
  - Agreements contain provisions for actions in event of business closure or bankruptcy of the third party
    - ensure access is maintained, and data transferred before cessation of business activities.

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Training in good data and record management

- Personnel should be trained in data integrity policies and agree to abide by them
- Trained to distinguish between proper and improper conduct, including deliberate falsification, and should be made aware of the potential consequences
- Key personnel, including managers, supervisors and quality unit personnel, should be trained in measures to prevent and detect data issues.
- Induction training and periodic retraining, as needed, should be done

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Addressing data reliability issues

- Examine potential impact of issues on patient safety and product quality and on the reliability of information used for decision-making and applications
- Notify health authorities if investigation identifies material impact on patients, products, reported information or on application dossiers
- Ensure that copies of all data are secured in a timely manner to permit a thorough review of the event and all related processes
- Interview people involved to better understand the nature of the failure and how it occurred and what might have been done to prevent and detect the issue sooner
- Consider impact beyond the specific issue identified, e.g., on previous decisions based upon the data and systems now found to be unreliable.
- Understand the underlying root cause(s) of the issue
- Take corrective and preventive actions not only address the identified issue, but also previous decisions and datasets that are impacted, as well as deeper, underlying root causes to prevent risks from recurring in the future.

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Good documentation practices

Good documentation practices (GDocP) is the basic building blocks of good PV data

Documentation should have the characteristics of being attributable, legible, contemporaneously recorded, original and accurate **(ALCOA).** These essential characteristics apply equally for both paper and electronic records

- **Attributable**. means information is captured in the record so that it is uniquely identified as executed by the originator of the data (e.g., a person or a computer system).
- **Legible, traceable and permanent**: refer to the requirements that data are readable, understandable, and allow a clear picture of the sequencing of steps or events in the record so that all GXP activities conducted can be fully reconstructed by the people reviewing these records.
- **Contemporaneous**: data recorded at the time they are generated or observed.
- **Original**: include the first or source capture of data or information and all subsequent data required to fully reconstruct the conduct of the activity.
- **Accurate**: data are correct, truthful, complete, valid and reliable.

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ALCOA Implementation: Attribution

Paper records

- initials;
- full handwritten signature;
- personal seal;
- date and time.

Electronic records:

- unique user logons and access control;
- unique electronic signatures;
- an audit trail that should capture user identification (ID) and date and time stamps;
- signatures, which must be securely and permanently linked to the record being signed.

Above are examples only.

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ALCOA Implementation: Legible, traceable and permanent

Paper records

- use of permanent, indelible ink;
- no use of pencil or erasures;
- use of single-line cross-outs to record changes with name, date and reason;
- no use of opaque correction fluid;
- controlled issuance of bound, paginated notebooks with sequentially numbered pages;
- archival of paper records by independent, designated personnel in secure and controlled paper archives

Above are examples only.

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ALCOA Implementation: Legible, traceable and permanent (contd)

Electronic records:

- designing and configuring computer systems with instant autosave;
- use of secure, time-stamped audit trails that record operator actions;
- configuration to restrict access to enhanced security permissions (such as the system administrator), only to persons independent of those responsible for the content;
- configuration to prohibit ability to overwrite data;
- validated backup of electronic records to ensure disaster recovery;
- validated archival of electronic records by independent, designated archivist(s) in secure and controlled electronic archives.

Above are examples only.

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ALCOA Implementation: Contemporaneous

Paper records:

- SOP, and training that ensure personnel record data entries *at the time of the activity directly in official controlled documents* (e.g., AEFI case report forms);
- SOP requiring that activities be recorded in paper records with the date of the activity;
- Good document design, which encourages good practice:

Above are examples only.

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ALCOA Implementation: Contemporaneous (contd)

Electronic records:

- configuration and SOPs that ensure data recorded in temporary memory are committed to durable media upon completion of the step or event and before proceeding to the next step or event in order to ensure the permanent recording of the step or event at the time it is conducted;
- secure system time/date stamps that cannot be altered by personnel;
- availability of the system to the user at the time of the activity.

Above are examples only.

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ALCOA Implementation: Original

Paper records:

- SOP and training to ensure adequate review and approval of original paper records;
- Documentation of data review (peer review). Signing the paper records that have been reviewed. Where record approval is a separate process, this should also be similarly signed.
- A procedure describing the actions to be taken if data review identifies an error or omission.

Above are examples only.

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ALCOA Implementation: Original (contd)

Electronic records:

- SOP and training that ensure personnel conduct an adequate review and approval of original electronic records, including human readable source records of electronic data;
- data review procedures describing review of original electronic data and relevant metadata.
- documentation of data review. For electronic records, this is typically signified by electronically signing the electronic data set that has been reviewed and approved.
- A procedure describing the actions to be taken if data review identifies an error or omission. Procedure should enable data corrections providing visibility of the original record and audit trailed traceability of the correction

Above are examples only.

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ALCOA Implementation: Retention of original records

Paper records:

- Controlled and secure storage areas, including archives, for paper records;
- Roles and responsibilities for archiving PV records should be defined in SOP and monitored;
- indexing of records to permit ready retrieval;
- periodic tests at appropriate intervals based upon risk assessment, to verify the ability to retrieve archived paper or static format records;.

Above are examples only.

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ALCOA Implementation: Retention of original records (contd)

Electronic records:

- routine back-up copies of original electronic records stored in another location as a safeguard in case of disaster;
- controlled and secure storage areas, including archives, for electronic records;
- indexing of records to permit ready retrieval;
- periodic tests to verify the ability to retrieve archived electronic data from storage locations;
- provision of suitable reader equipment, such as software, operating systems and virtualized environments, to view the archived electronic data when required;

Above are examples only.

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ALCOA Implementation: Accurate

Paper and Electronic records:

- validation of computerized systems that generate, process, maintain, distribute or archive electronic records;
- systems must be validated to ensure their integrity while transmitting between computerized systems;
- review of PV records;
- investigation of deviations and doubtful and out-of-specifications results.

Above are examples only.

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Compliance monitoring and system performance

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Compliance management by marketing authorization holders

MAH should have specific quality system procedures and processes in order to ensure the following:

- **continuous monitoring** of PV data, the examination of options for risk minimization and prevention and that appropriate measures are taken by the MAH
- **scientific evaluation** of all information on the risks of medicinal products as regards patients' or public health
- **submission of accurate and verifiable data** on serious and non-serious adverse reactions to the competent authorities within the legally required time-limits
- the **quality, integrity and completeness** of the information submitted on the risks of medicinal products

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Compliance management by marketing authorization holders (contd.)

MAH should have specific quality system procedures and processes in order to ensure the following:

- **effective communication** by the MAH with competent authorities, including communication on new or changed risks, risk management systems, risk minimization measures, periodic safety update reports, corrective and preventive actions and post-authorization safety studies
- **update of product information** by the MAH in the light of scientific knowledge
- **appropriate communication** of relevant safety information **to healthcare professionals and patients**

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Monitoring of the performance and effectiveness of the PV system

Processes include:

- reviews of the systems by those responsible for management;
- audits;
- compliance monitoring;
- inspections;
- evaluating the effectiveness of actions taken with medicinal products for the purpose of minimizing risks and supporting their safe and effective use in patients.

The organization may use **performance indicators** to continuously monitor the good performance of pharmacovigilance activities

Pre-defined procedure for the review of the system should be in place

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Example: Monitoring of the performance and effectiveness of PSUR development process

- ❑ written **SOP** for PSUR preparation, quality control, review and submission
- ❑ PSUR **document template** could be developed to ensure completeness of data
- ❑ Data included in the summary tabulations should undergo **source data verification** against the MAH's safety database to ensure accuracy of the number of events provided
- ❑ Develop quality system to avoid failure to comply with PSUR requirements such as:
  - non-submission, or submission outside the correct submission schedule or outside the correct time frames
  - unjustified omission of information
  - poor documentation or insufficient information
  - previous requests from competent authorities not addressed
  - failure to provide an explicit evaluation of the risk-benefit balance of the medicinal product
  - failure to provide adequate proposals for the local authorized product information

PSUR, or PBRER

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Practical Tips and Take-home Points

- ❑ Quality can not be assured in a regulated industry without good documents and good documentation practices
- ❑ Just creating documents is not enough; you must follow specific standards when doing so.
- ❑ It is necessary to document anything that directly impacts a product and activity
- ❑ Manufacturers should consider developing the following:
  - ✓ SOPs and work instructions
  - ✓ pharmacovigilance system master file (PSMF)
  - ✓ job descriptions and Curriculum Vitae in standard format
  - ✓ organizational chart
  - ✓ Pharmacovigilance policy
- ❑ Manufacturers should consider having following processes to ensure compliance monitoring:
  - ✓ Audit plan
  - ✓ Product/vaccine safety committee
  - ✓ AEFI review committee
  - ✓ Quality control/review checklists
  - ✓ Standard monthly/weekly compliance report format
  - ✓ Performance metrics/Key performance indicators

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Thank You

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