15th July 2021

Safety database operation, validation, back-up, disaster recovery, including Expedited reporting to Regulatory Authorities

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Flow of this Presentation

General Procedures for collection, management and reporting of suspected adverse reactions

Structure and processes

Database in Pharmacovigilance – Regulatory Requirements

Choice of Database and Best practices for use of database in pharmacovigilance

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Important Terminologies

❑ **Individual Case Safety Report (ICSR):**

➢ This refers to the format and content for the reporting of one or several suspected adverse event in relation to a medicinal product <u>that occur in a single patient at a specific point of time</u>.

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MAH's Responsibilities

❑ Have **system and established procedures** for collecting and recording of all suspected reports <u>irrespective of the source,</u> means, etc.

❑ **Develop** PV system that
➢ ensures the collected reports are authentic, legible, accurate, consistent, verifiable and as complete as possible
➢ capable of acquiring sufficient information for the scientific evaluation of the reports

❑ **Establish** mechanisms that enables <u>traceability and follow-up</u> of report while complying with the data protection legislation

❑ **Retain** PV data and documents as long as the product is authorised and later after the authorisation has ceased to exist as per applicable regulatory requirements

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Adverse Reaction Report Management

1. Collection
2. Validation
3. Follow-up
4. Data Management
5. Quality Management
6. Reporting Time frames and Modalities

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Collection

❑ **Unsolicited Reports**

➢ *Spontaneous reports*
- o Received from Health Care Professional (HCP) or consumer
- o **Reports of Quality Defect -** report valid ICSR associated with quality defect

➢ **Regulatory Authority Reports**
- o Maybe bulk reports (multiple ICSRs)
- o Follow up is generally difficult to perform

➢ *Literature reports*
- o Search articles containing adverse events with suspected product belonging to the company
- o The scientific and medical literature including abstracts, manuscripts etc.

➢ *Other source* – non-medical entity e.g., lay press, media, etc.
➢ *Internet or digital media* under the MAH's management or responsibility

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Validation

❑ Only valid ICSRs qualify for reporting

❑ The details required for report qualification include:

Identifiable Reporter i.e. primary source (one or more)	Identifiable Patient (single)	Suspected Medicinal Product	Suspected Adverse Reaction
• Name, initial or address and qualification (e.g., physician, other HCP, lawyer, consumer or other non-HCP) • Contact number for follow-up purpose • Author – literature reports	• Initials, patient identification number, date of birth, age, age group or gender	• one or more	• one or more • Causal relationship determination by reporter

❖ **Both valid and invalid ICSR should be recorded within the PV system for on-going safety evaluation purpose**

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Follow-up

- ❑ In addition to minimum information collection, the ***follow up / monitoring*** should be done for the events with

  - ➢ special interest
  - ➢ prospective reports of pregnancy
  - ➢ cases notifying the death
  - ➢ cases reporting new risks or changes in the known risks

- ❑ The follow up ***methods***

  Should:
  - ➢ be tailored towards optimising the missing information collection process,
  - ➢ encourage the reporter to submit any new relevant information, and
  - ➢ make use of target-specific forms in the local language

  Should not:
  - ➢ request the reporter to repeat information already provided or
  - ➢ have extensive questionnaires

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Follow-up…

- ❑ For information which is ***received directly from a consumer***

  - ➢ Attempt to obtain follow up information from Health Care Professional (HCP) after consent
  - ➢ Subsequent confirmation (totally or partially) by a HCP, if any, should be clearly highlighted in the ICSR

- ❑ Any ***attempt*** to obtain follow-up information should be ***documented***

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Data Management

- ❑ **Electronic data** and **paper reports** should be stored, transfer and treated in such as way that
  - ➢ it maintains *confidentiality* of the patients' and reporters'
- ❑ Ensuring *security and non-corruption* of data during transfer
- ❑ Have **strict access controls** and available to **authorised personnel only**
- ❑ The data/report received should be:
  - ➢ treated in an *unbiased* and *unfiltered* way
  - ➢ *coded* using appropriate terminology and
  - ➢ includes the *verbatim text* or *accurate translation* of the information
- ❑ **Quality Control** to verify correct data entry, including the appropriate use of terminologies
- ❑ During data entry and aggregated reports generation, there should be procedure for identification and management of **duplicate cases**

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Quality Management

- ❑ A **quality management system** should be in place to ensure compliance with necessary quality standards at every stage of case management
- ❑ **Quality control procedures** should be implemented for the verification of the stored data against the initial and follow-up reports
- ❑ There should be **clear written SOP's** pertaining to:
  - ➢ role and responsibilities and task specific to the respective parties involved
  - ➢ provision for proper control and change of the system and
  - ➢ activities including those contracted to third parties
- ❑ **Trainings**
  - ➢ Task-specific training
  - ➢ Current PV legislation and guidelines

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Reporting

❑ ICSRs with the minimum required information are valid and reportable

❑ **Day Zero** – the reporting **time clock starts** as soon as the minimum information is received

➢ For literature report, day zero is when one becomes aware of the publication with the minimum required information

❑ **Time Frame:** Depends on the region/country requirements *(kindly check local regulations)*

➢ For serious ICSR – **15 calendar days** after initial receipt of information
    ○ applicable for both initial and follow-up information
    ○ applicable for report where initial case of serious nature changed to non-serious in follow-up information
    ○ May depend on expectedness and causality of events

➢ For non-serious ICSR – **90 days** from the date of receipt of the reports
➢ ICSRs from foreign countries - also required to be reported in many countries

❑ **Modalities:** Depends on the regional/country requirements

➢ **Electronically**
➢ **Paper based submission**

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ICSR format is precise and exacting and includes:

References for administration and identification purposes, including where the report came from and who received it

All information from primary sources

Characteristics of the patient concerned

Description of the relevant events

Results of clinical tests and procedures

Characteristics of the medicinal product in question

Narrative style summary of the case

Any further relevant supporting information

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Each ICSR should be:

o Validated before reporting

o Submitted within extremely strict and rapid timescales – starting from the time when minimal information is brought to attention of the MAH

o Rapidly re-submitted as new or updated information becomes available which has an impact on the original submission

o Ensure Safety Data Exchange Agreements (SDEAs) exist regarding relevant information exchanges

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Pharmacovigilance Information Flow

AE Case Reception:
- Receive AE case
- Document receipt
- Index, file source documents

AE Case Triage
- Identify duplicate AE Case
- Assign case priority
- Enter other case data into database
- Perform quality check of data entered

Event Assessment
- Prepare company narrative for review
- Assess case from medical perspective
- Perform final review of case for reportability

Processing Follow-up information
- Identify additional information required to analyze/report the case
- Follow-up with case reporter to obtain additional information
- Update information in database

Risk/Benefit Analysis
- Perform R/B analysis based on data
- Prepare Analysis report

Regulatory Submission
- Prepare safety report
- Facilitate final review
- Submit report to CA
- Track submission date of report

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Receipt

- Any source, All reporters:
  - including salespersons and other company staff
  - Use standard forms, dedicated telephone number, email id etc.
  - Monitor company website, social media sites, fax, mails, news, etc.
- All reports to be transmitted to the PV center
  - Enter reports into the 'Receipt log'
  - Enters INITIAL RECEIPT DATE and time (Day zero and Time zero) with signatures.
  - Reporting timelines are calculated from the INITIAL RECEIPT DATE

LogBook

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Receipt Unique ID

o   A receipt UID is assigned for each report in the receipt log

o   In case of received regulatory line listings, the email and the column containing regulatory UIDs may be printed and entered into the receipt log with a single UID for all cases

	ID
1	669DDCB5-472B-4159-9CE5-004EBB43DD3A
2	CF2FE948-0CC6-40AF-BC04-005A227E5334
3	8C6FDC62-D9AD-47C4-8B76-008C858C15C6

	ID
1	4B55D85B-BE8F-DD11-9FD6-001BFC06E612
2	4C55D85B-BE8F-DD11-9FD6-001BFC06E612
3	4D55D85B-BE8F-DD11-9FD6-001BFC06E612

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Triage

❑ Triage is the assessment, classification and prioritization of the information received according to key regulatory, scientific and medical criteria.

Adverse event report may be placed into one of the following categories:

1) Non-serious case
2) Serious case
3) No case (minimum criteria for an AE case are not fulfilled)
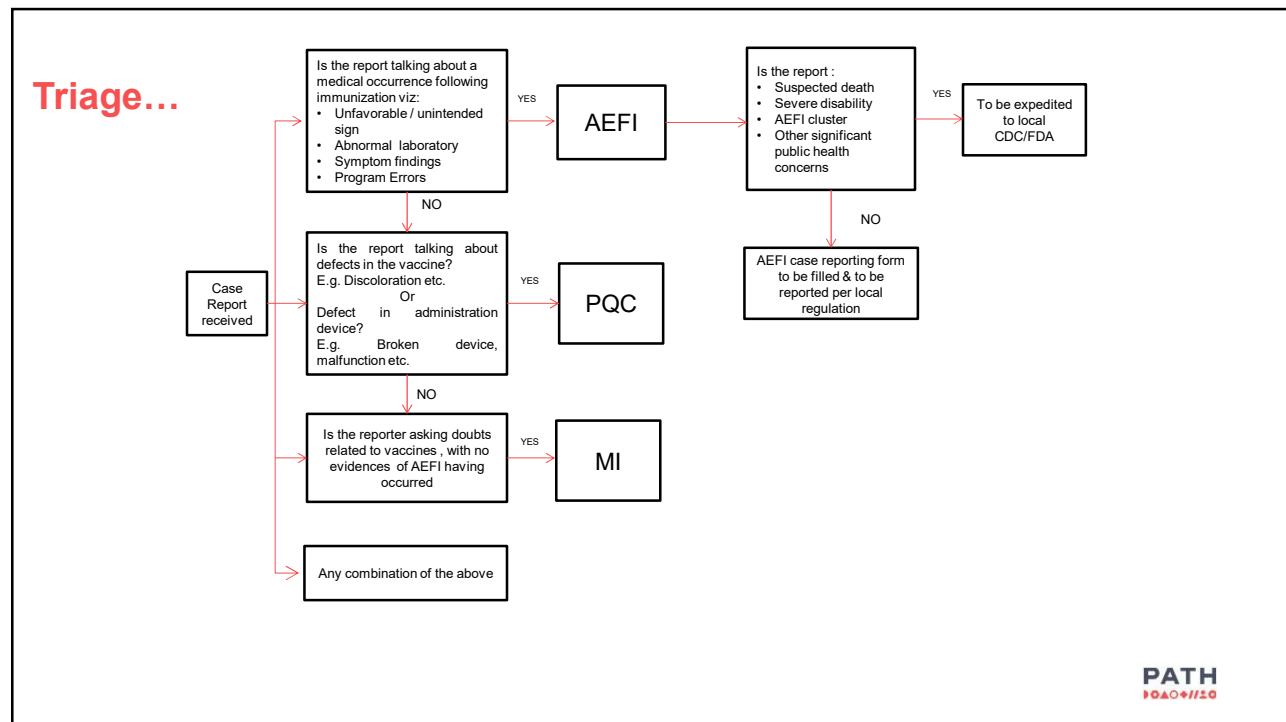4) Product quality related issues and/or medical inquiries.

If the reports have not been received in the standard AEFI, PQC or MI forms, enter the received data into standard forms

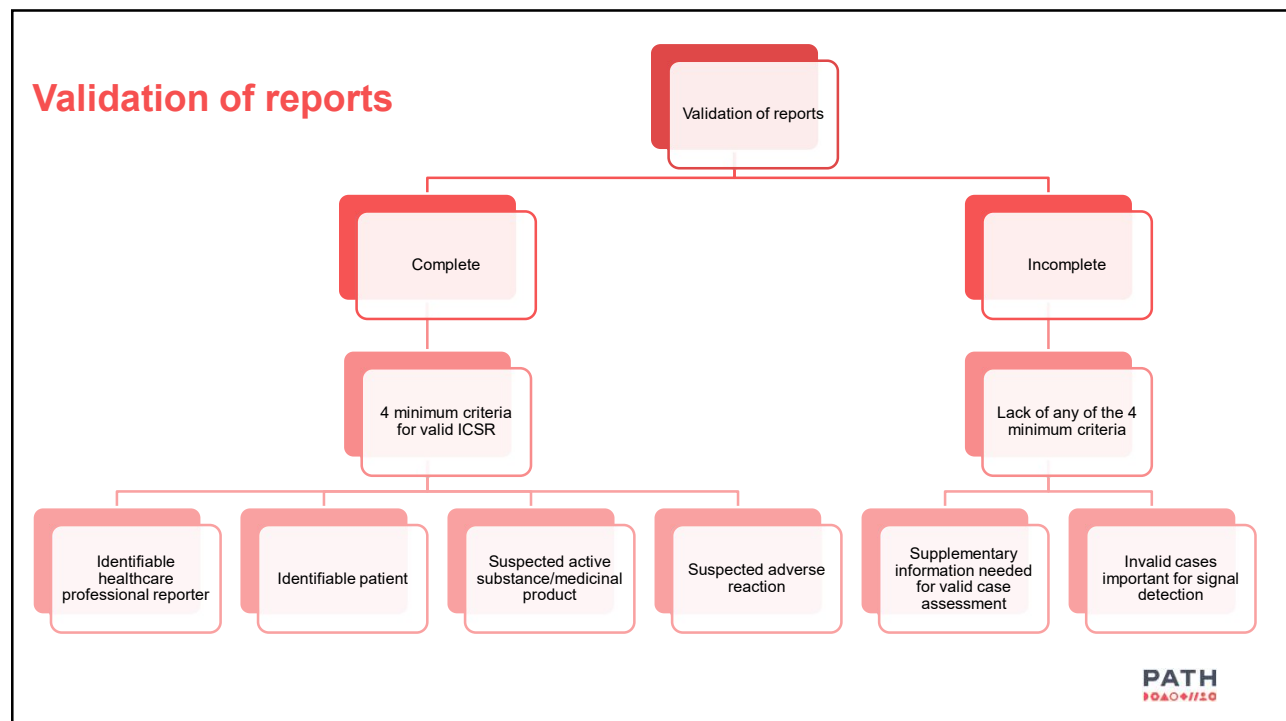Triage errors if not corrected in time leads to:
Late regulatory reports &
Missed safety signals

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Triage…

```
Case Report received
```

Is the report talking about a medical occurrence following immunization viz:
• Unfavorable / unintended sign
• Abnormal laboratory
• Symptom findings
• Program Errors

→ YES → **AEFI**

Is the report :
• Suspected death
• Severe disability
• AEFI cluster
• Other significant public health concerns

→ YES → To be expedited to local CDC/FDA

↓ NO

AEFI case reporting form to be filled & to be reported per local regulation

↓ NO

Is the report talking about defects in the vaccine? E.g. Discoloration etc.
Or
Defect in administration device? E.g. Broken device, malfunction etc.

→ YES → **PQC**

↓ NO

Is the reporter asking doubts related to vaccines , with no evidences of AEFI having occurred

→ YES → **MI**

Any combination of the above

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Validation of reports

```
Validation of reports
├── Complete
│   └── 4 minimum criteria for valid ICSR
│       ├── Identifiable healthcare professional reporter
│       ├── Identifiable patient
│       ├── Suspected active substance/medicinal product
│       └── Suspected adverse reaction
└── Incomplete
    └── Lack of any of the 4 minimum criteria
        ├── Supplementary information needed for valid case assessment
        └── Invalid cases important for signal detection
```

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Duplicate Check

A duplicate check is performed, and it is determined if new case creation criteria are met

If case creation criteria are met, a UID is assigned in the safety database.
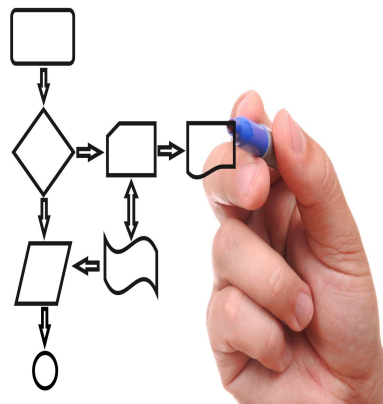
- Different than Receipt UID

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Case Processing

The reports are then processed in the safety database

Company must ensure that all reports are processed within stipulated timelines

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Data Entry

<u>Chief data entry fields</u>

Patient details
- Initials, age, sex, date of birth, height and weight, autopsy details in case of death cases
- Medical, social and family history

Reporter details
- Name, qualification (HCP/Non-HCP), address and region

The suspect and concomitant vaccines
- Brand, manufacturer,
- dose,
- formulation,
- route of administration,
- action taken with the vaccine
- Indication
- Batch information

Adverse Events
- The appropriate AEFIs are selected for MedDRA coding
- The events are assigned seriousness, the start and stop dates are entered if provided and the outcome is assigned for each event.
- Laboratory investigations relevant to the event are entered if provided in the source documents

Safety Narrative
- A complete safety narrative is written
- The case is then sent to next step in the process

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Quality Review

❑ May happen before or after the Medical Review – depends on company SOP

❑ Another associate checks the case for completeness and accuracy

❑ If found satisfactory, the case is then routed to the next step

❑ If the quality is not satisfactory, the case is sent back to data entry

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Medical Review

The following actions are verified in this step:

- Appropriate selection of AEFIs and MedDRA coding of the same is completed
- Appropriate selection of suspect and concomitant vaccines
- If needed, additional AEFIs can be added
- Any concomitant vaccine can be upgraded to a suspect vaccine or vice versa with suitable rationale
- Review seriousness assessment
- Perform an expectedness assessment using the Pack Insert
- Perform an event assessment as follows:
  - Causality assessment between the event(s) and the vaccine
  - Analyze if the event(s) exceed the normal reporting rates
  - impact on current safety profile of the product
  - Review of case for regulatory reporting
- Prepare company narrative based on received information

Med = Medical
D = Dictionary for
R = Regulatory
A = Activities

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Medical Review…

Case Narrative, Causality Assessment and Comments

❑ For all cases, except non-serious, **a case narrative** should be provided that could serve as a comprehensive, stand-alone "medical report" containing all relevant information

❑ The **information provided in the narrative** should be:

  ➢ a logical time sequence and

  ➢ the chronology of the patient's experience including a summary of any relevant autopsy or post-mortem findings

❑ '**Reporter's comments**' – include primary source's comment, if available, on the diagnosis, causality assessment or other relevant issue

❑ '**Sender's comments**' –

  ➢ disagreement - include case assessment and any disagreement with and/or alternatives to the reported diagnoses

  ➢ emerging safety issue – provide a summary of the points of concerns and actions proposed

❑ '**Relatedness of drug to reaction(s)/event(s)**' – indicate the degree of suspected relatedness

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Reporting of ICSRs

- **Check local regulations**
- **Exchange with business partners per the agreement**

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Follow-up Reports

- Follow-up methods should be tailored towards optimizing the collection of missing information
- Target submission of new information only
- Seek medical confirmation of consumer reports

Incomplete reports
Missing minimum information
Supplementary detailed information
Events monitored with special interest
Prospective reports of pregnancy cases
Cases notified patients death
Cases reporting new risks/ changes in known risk

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Follow-up Reports…

- Follow-up procedure clearly documented in SOP

- Define regular intervals for requesting follow-up information

  - Serious reports
  - Non serious reports
  - Pregnancy cases
- New information should be clearly identifiable in the case narrative

- Report follow-up information if significant new medical information has been received

  - new suspected adverse reaction(s)
  - change in the causality assessment
  - new or updated information on the case that impacts on its medical interpretation
  - Seriousness and/or causality assessment downgraded

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Acknowledgement

- An acknowledgment form is dispatched to the sender of the report

- If a case had been created, the UID can also mentioned in the acknowledgment form

- The source documents along with the sent acknowledgements are filed

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Record retention and Tracking

- ❑ Archive a copy of the received data along with the source documents and the sent acknowledgments
- ❑ Address missing reconciliation queries in case these are received from the sender

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Reconciliation

ICSR Reconciliation – Database

A thorough review of the safety database is performed at set interval to ensure that there are no missing data or discrepancies

Tracking and Metrics: It is critical that all cases reports be tracked

ICSR Reconciliation – Business Partners

Provide CIOMS II line listing to all appropriate partners

If an ICSR is listed, but has not been received by any of the partner(s), it shall be promptly resent

This process will be closed and completed when the other party confirms the receipt of all the cases listed

A Reconciliation tracker can be maintained to track & monitor the compliance.

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Flow of this Presentation

General Procedures for collection, management and reporting of suspected adverse reactions
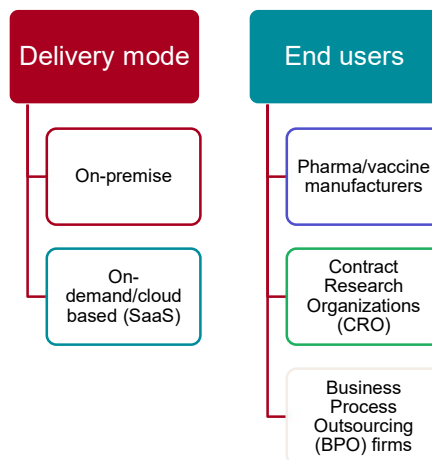
Structure and processes

Database in Pharmacovigilance – Regulatory Requirements

Best practices for use of database in pharmacovigilance

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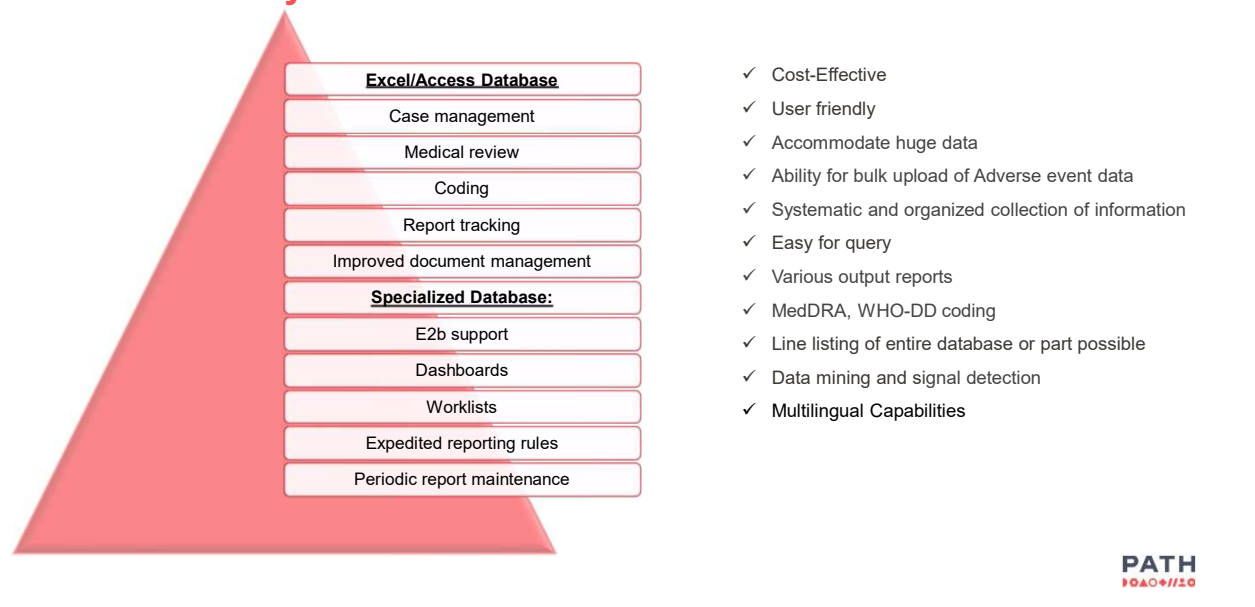# Database: Global software market

Delivery mode	End users
On-premise	Pharma/vaccine manufacturers
On-demand/cloud based (SaaS)	Contract Research Organizations (CRO)
	Business Process Outsourcing (BPO) firms

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Database: Utility and Desirable Traits

Excel/Access Database
Case management
Medical review
Coding
Report tracking
Improved document management
Specialized Database:
E2b support
Dashboards
Worklists
Expedited reporting rules
Periodic report maintenance

- ✓ Cost-Effective
- ✓ User friendly
- ✓ Accommodate huge data
- ✓ Ability for bulk upload of Adverse event data
- ✓ Systematic and organized collection of information
- ✓ Easy for query
- ✓ Various output reports
- ✓ MedDRA, WHO-DD coding
- ✓ Line listing of entire database or part possible
- ✓ Data mining and signal detection
- ✓ Multilingual Capabilities

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Electronic PV Database: Regulatory Requirements

➤ Should be validated

➤ Should not decrease product quality, process control or quality assurance, or increase in overall risk of the process

General

1. *Risk Management*

   ❑ Extent of validation and data integrity controls based on risk assessment of the computerized system.

2. *Personnel*

   ❑ Close cooperation between all relevant personnel. Appropriately qualified, with defined responsibilities.

3. *Suppliers and Service Providers*

   ❑ Formal agreements are a must
   ❑ Competent and reliable. Consider an audit based on a risk assessment
   ❑ Thorough review of documentation to ensure user requirements are fulfilled

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Electronic PV Database: Regulatory Requirements…

Project Phase

❑ 4. *Validation*

    ❑ Validation documentation and reports should cover relevant steps of the life cycle

    ❑ User Requirements Specifications should describe the required functions and should be traceable throughout the life-cycle

    ❑ System should be developed in accordance with an appropriate quality management system.

    ❑ Evidence of appropriate test methods and test scenarios should be demonstrated

    ❑ If data are transferred to another data format or system, validation should include checks that data are not altered in value and/or meaning during this migration process

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Electronic PV Database: Regulatory Requirements…

Operational Phase

5. *Data*

    ❑ Systems exchanging data electronically with other systems should include appropriate built-in checks for correct and secure entry and processing of data

6. *Accuracy Checks*

    ❑ Additional check on the accuracy of the data by a second operator or by validated electronic means

7. *Data Storage*

    ❑ Data should be secured by both physical and electronic means against damage.

    ❑ Stored data should be checked for accessibility, readability and accuracy.

    ❑ Access to data should be ensured throughout the retention period.

    ❑ Regular back-ups of all relevant data should be done.

    ❑ Integrity and accuracy of backup data and the ability to restore the data should be checked during validation and monitored periodically.

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Electronic PV Database: Regulatory Requirements…

8. *Printouts*

❑ Should be possible to print electronically stored data

9. *Audit Trails*

❑ System should create record of all relevant changes and deletions ("audit trail").
❑ For change or deletion, the reason should be documented.
❑ Audit trails need to be regularly reviewed

10. *Change and Configuration Management*

❑ Any changes including system configurations should only be made in a controlled manner in accordance with a defined procedure.

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Electronic PV Database: Regulatory Requirements…

11. *Periodic evaluation*

❑ Periodically evaluated to confirm that they remain in a valid state.
❑ Evaluations should include - current range of functionality, deviation records, incidents, problems, upgrade history, performance, reliability, security and validation status reports

12. *Security*

❑ Physical and/or logical controls to restrict access to computerized system to authorized persons. (use of keys, pass cards, personal codes with passwords, biometrics, restricted access to computer equipment and data storage areas)
❑ Creation, change, and cancellation of access authorizations should be recorded

13. *Incident Management*

❑ All incidents, not only system failures and data errors, should be reported and assessed
❑ Root cause of critical incident should be identified and lead to corrective and preventive actions

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Electronic PV Database: Regulatory Requirements…

14. *Electronic Signature*

- ❑ Electronic records may be signed electronically.
- ❑ Electronic signatures are expected to:
  - ❑ have the same impact as hand-written signatures within the boundaries of the company
  - ❑ be permanently linked to their respective record
  - ❑ include the time and date that they were applied

15. *Archiving*

- ❑ Data may be archived.
- ❑ Should be checked for accessibility, readability and integrity

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Electronic PV Database: Regulatory Requirements…

16. *Business Continuity*

- ❑ Provisions should be made to ensure continuity of support for those processes in the event of a system breakdown (e.g., a manual or alternative system).
- ❑ These arrangements should be adequately documented and tested.

More information/Further Reading:
EudraLex: The Rules Governing Medicinal Products in the European Union Volume 4
Good Manufacturing Practice
Medicinal Products for Human and Veterinary Use
Annex 11: Computerized Systems

USFDA 21 CFR
Part 11, Electronic Records; Electronic Signatures - Scope and Application

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Disaster Recovery – In brief

❑ **Disaster Recovery**
- Organization's ability to respond to and recover from an event that negatively affects business operations.
- DR is a subset of business continuity that focuses on the IT systems that enable business functions.

❑ **Goal**
- To enable organization to regain use of critical systems and IT infrastructure as soon as possible after a disaster occurs.

❑ **Disaster recovery plan**
- Perform an in-depth analysis of systems and create a **formal document** to follow in times of crisis.

❑ **Type of Disaster**
- Cyber attacks such as malware, DDoS and ransomware attacks
- Sabotage
- Power outages
- Equipment failure
- Epidemics or pandemics, such as COVID-19
- Industrial accidents
- Hurricanes, Tornadoes, Earthquakes, Floods, Fires

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Database in Pharmacovigilance – Regulatory Requirements

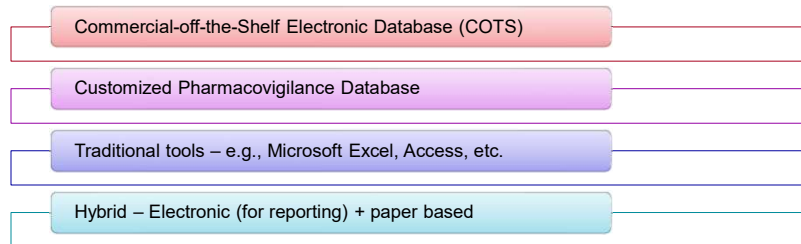Choice of Database and Best practices for use of database in pharmacovigilance

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Choice of Database

Specialized, commercial PV database are expensive. Choice of Database may depend on:

❑ Cost

❑ Number of ICSR cases – current and future

❑ Hosting models

❑ Prior experience - regulatory

❑ Compatibility and interoperability

| Commercial-off-the-Shelf Electronic Database (COTS) |
| Customized Pharmacovigilance Database |
| Traditional tools – e.g., Microsoft Excel, Access, etc. |
| Hybrid – Electronic (for reporting) + paper based |

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MS Excel as a Database: Considerations

❑   MS Excel is an electronic application. Hence, the regulations/guidelines apply

❑   Some issues to be addressed:

   ❑   Not 21 CFR Part 11- compliant (e.g., no audit trail)
   ❑   Files may become corrupted and can critical data may get lost
   ❑   Analysis of data can be difficult
   ❑   Electronic reporting not possible

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MS Excel as a Database: Considerations…

Some ways to address the issues:

❑ Increase security

  ❑ Restrict use to intended user
  ❑ Save Excel on a server location and apply access control to named users
  ❑ Use password to protect the spreadsheet – separate password for read and modify
  ❑ Lock cells except selected ones
  ❑ Use colors for clarity
  ❑ Drop-down menus or data entry limits may help prevent entry mistakes
  ❑ Implement version number for change control

❑ Create regular back-up copy

❑ Verify data manually and document reliability of the spreadsheet

❑ Prepare and follow robust Standard Operating Procedures

  ❑ Include: change and configuration management, backup and restore, and archiving and retrieval.

❑ Prepare and follow Working Instructions on how to use based on type of user

❑ Involve statistician to increase usability and ability for data mining

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Best Practices

➢ Record all PV information

➢ Apply Principles of good data and record management practices to both paper and electronic data

➢ Record-keeping methodologies and systems, whether paper or electronic, should encourage compliance with the principles of data integrity.

➢ Periodically review record keeping systems for effectiveness and update as necessary

➢ Do not share unique user logons

➢ Maintain strict access control

➢ Maintain audit trail

➢ Keep configuration to prohibit ability to overwrite data

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Best Practices…

➢ Validate archival of electronic records by independent, designated archivist(s) in secure and controlled electronic archives

➢ Ensure availability of the system to the user at the time of the activity

➢ Ensure adequate SOP and training for review and approval

➢ Ensure adequate documentation of data review

➢ Routinely back-up copies of original electronic records in another location as a safeguard in case of disaster

➢ Controlled and secure storage areas, including archives, for electronic records;

➢ Index records to permit ready retrieval

➢ Investigate deviations and doubtful and out-of-specifications results

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Thank You

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