Module 5: Literature Search

Introduction

- Information about new ADRs may also appear as published case reports or clinical studies.
- Scientific and medical literature is
  - An important source of information on suspected ADRs
  - A significant source of information for the monitoring of the safety profile and risk-benefit balance of medicinal products,
  - For detection of new safety signals or emerging safety issues
- Literature screening is mandatory to address the legal regulatory requirements

Objectives

Why do we review literature- Regulatory Requirement

- ✓ Pharmaceutical companies need to screen scientific literature and triage for adverse events related to `their products so that they can be promptly reported for regulatory compliance
- ✓ Review literature for each product and identify articles for signal detection purposes
- ✓ To address legal requirements per EMA and FDA regulations and for inclusion in both the DSUR and the PBRER.

When to start and stop searching in the scientific and medical literature ?

- ✓ Literature searching would start on submission of a marketing authorization application and continue while the authorization is active.

Where to look ?

- ✓ Articles relevant to the safety of medicinal products are usually published in well-recognized scientific and medical journals.

Methodology (1)

- It is the responsibility of the MAH to ensure that the world wide literature is searched.
- Database to be searched
  - Embase
  - Journals covered by EBSCO
  - SEDBASE
  - TOXLINE
- The usual frequency for literature search is once a month. However, some countries within Europe allow a longer interval for generic companies, may be as long as once in 3 months.
- The search should include the entire product list of the MAH

Methodology (2)

Criteria for literature searching

- Pharmaceutical companies are required to search global literature to ensure that all publications relevant for safe administration of a medicinal product are duly captured.
- The common search terms used are:
  - Overdose
  - drug abuse
  - Dependence
  - Pregnancy
  - Lactation
  - lack of efficacy
  - Contraindications
  - drug interactions
  - food-drug interactions
  - fatal

Pubmed

- **PubMed** is a free search engine accessing primarily the MEDLINE database of references and abstracts on life sciences and biomedical topics.
- The United States National Library of Medicine (NLM) at the National Institutes of Health maintains the database as part of the Entrez system of information retrieval.
- PubMed, first released in January 1996, ushered in the era of private, free, home- and office-based MEDLINE searching..
- In addition to MEDLINE, PubMed provides access to:
  - Older references from the print version of *Index Medicus* back to 1951 and earlier;
  - References to some journals before they were indexed in Index Medicus and MEDLINE, for instance *Science*, *BMJ*, and *Annals of Surgery*;
  - A collection of books available full-text and other subsets of NLM records.
  - PMC citations

MEDLINE & EMBASE

Medline (Medical Literature Analysis and Retrieval System Online, or MEDLARS Online)

- A bibliographic database of life sciences and biomedical information.
- It includes bibliographic information for articles from academic journals covering medicine, nursing, pharmacy, dentistry, veterinary medicine, and health care.
- MEDLINE also covers much of the literature in biology and biochemistry, as well as fields such as molecular evolution.
- Medline is compiled by the United States National Library of Medicine (NLM), MEDLINE is freely available on the Internet and searchable via Pub Med and NLM's National Centre for
- **Embase (for Excerpta Medica dataBASE)**
- A biomedical and pharmacological database of published literature designed to support information managers and pharmacovigilance in complying with the

  regulatory requirements of a licensed drug.
- Embase, produced by Elsevier, contains over 28 million records from over 8,400 currently published journals from 1947 to the present

Points to consider while conducting literature searches using search engines

- **Use of Boolean Operators**
  - AND (default Boolean operator)
  - OR
  - NOT
  - Should be capitalized always
- **Use of parentheses to create an order of operations**
  - Operations inside the parentheses will be done before the operation between the different sets of terms
- **Applying limits**
  - Time period, language, article type, population, gender, etc.
- **Beware**
  - No documents found/ Your search retrieved zero results
  - Misspelled term, Boolean not capitalized - possible contributors

Review Process

Procurement of full articles and translations

- MAHs should also ensure that full publications are procured and translations are carried out promptly to facilitate review and regulatory reporting.
- Full publications need to be submitted with all expedited reports.

Criteria for literature searching

- Literature hits received include individual case reports, drug reviews, drug class reviews, metaanalyses and results of animal or clinical or comparative studies.
- Individual case reports need to be processed like ICSRs from other sources. Initial Receipt Date (IRD) – IRD for a literature hit is the data when MAH becomes aware of the publication (abstract or full) containing the minimum information for a valid case.
- All new information collected from publications must be reviewed in detail at the time of conducting routine benefit risk analysis and periodic reporting

Literature ICSR

For a Literature case to be considered a valid ICSR, four minimum criteria should be present

- **Identifiable reporter**
  - Person whose contact information is provided in abstract/article
  - If there is no contact information, then reporter is first author of literature article
  - Country of report is based on country of author of literature article
- **Identifiable patient**
  - One or more of following: Initials, date of birth, age or age category (i.e., child, adult, elderly), gender
  - Identifiable reporter provided sufficient clinical details to indicate the patient is real
- **Suspect product**
  - Literature article should have information regarding company's product – drug, form, strength
  - with same INN as company's brand or generic marketed by company
  - Combination product: company must have combination product registered and not only a single ingredient of combination An ICSR is not created for each single ingredient
  - Ownership of product cannot be excluded by the following, then assume a company's product:
    - Product source and/or invented name not specified
    - Active substance(s)
    - Formulation
    - Route of administration

Reaction/Event

Type of literature Articles

1. Meta-analysis
2. Clinical Studies
3. Observational studies
4. Review articles
5. Case reports
6. Others
   a) Poster presentation
   b) Meeting abstracts
   c) Pre-clinical studies

Important Types of literature Articles (1)

Meta-analysis

- A "meta-analysis" is a statistical approach to combine the data derived from a systematic-review. Therefore, every meta-analysis should be based on an underlying systematic review, but not every systematic review leads to a meta-analysis.
- Meta-analyses tend to have highest weightage when considering literature for signal detection and signal assessment.

Clinical Studies

- Randomized controlled trials (RCT): are often used to test the efficacy or effectiveness of various types of medical intervention and may provide information about adverse effects, such as drug reactions.
- Non-randomized studies are single arm studies

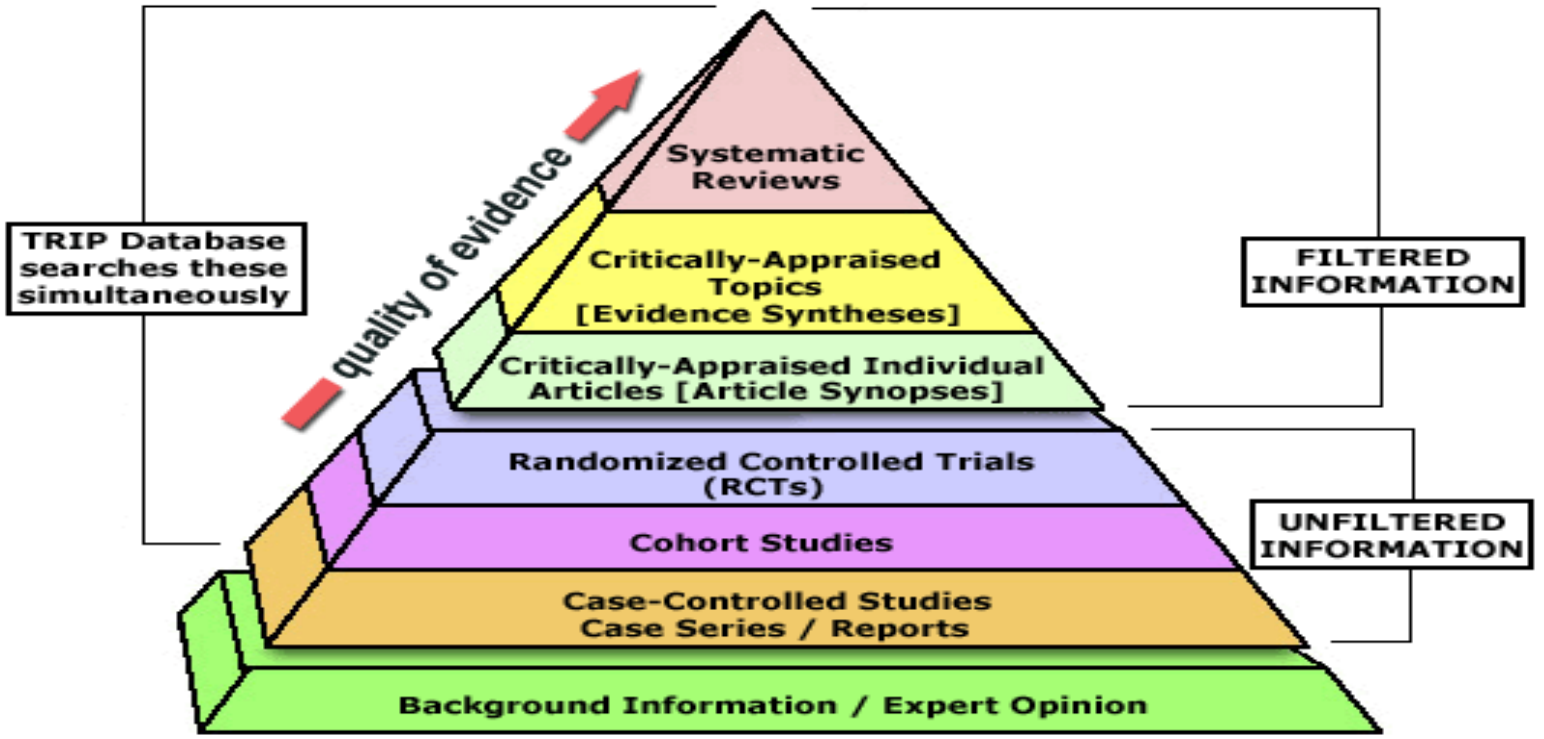
Important Type of literature Articles (2)

Review Articles

A systematic review is a thorough, comprehensive, and explicit way of interrogating the medical literature. It typically involves several steps, including (1) asking an answerable question (often the most difficult step), (2) identifying one or more databases to search, (3) developing an explicit search strategy, (4) selecting titles, abstracts, and manuscripts based on explicit inclusion and exclusion criteria, and (5) abstracting data in a standardized format.

- Case reports
  - These are literature articles pertaining to the one or more patients and provide details about the clinical course of the side effect with comorbid conditions and treatments provided.

Strength of Evidence



Medical Literature Monitoring (MLM) (1)

- To enhance the efficiency of reporting and to provide a simplification for pharmaceutical industry, EMA regulations say that
  - The Agency (EMA) shall monitor selected medical literature for reports of suspected adverse reactions to medicinal products containing certain active substances. It shall publish a list of active substances being monitored and the medical literature subject to this monitoring.
  - The Agency shall enter into the EudraVigilance database relevant information from the selected medical literature.
  - The Agency shall, in consultation with the Commission, Member States and interested parties, draw up a detailed guide regarding the monitoring of medical literature and the entry of relevant information into the EudraVigilance database.

- EMA's expectations are that MAHs shall not be required to resubmit ICSRs which have already been identified during MLM process. However, MAHs shall monitor all other medical literature and report any suspected adverse reactions.

Medical Literature monitoring (2)

- ICSRs resulting from the MLM service performed by the Agency can be accessed from the EudraVigilance database by the MAH concerned.
- They are also made available for download in XML format.
- This refers to ICSRs of serious suspected adverse reactions occurring within and outside the EU, and to ICSRs of non-serious suspected adverse reactions from within the EU.
- In order to avoid the submission of duplicate ICSRs, the MAHs shall only submit those ICSRs described in the medical literature which is not reviewed by the Agency, for all medicinal products containing active substances which are not included in the list monitored by the Agency.

Medical Literature monitoring (3)

Active substances are included in the MLM service?

- A range of active substance, including herbals, have been selected on the basis of medicinal product information submitted to EMA in line with Article 57(2), second subparagraph of Regulation (EC) No 726/2004.

- Active substances contained in medicines for which a high number of marketing authorisations were granted to various marketing-authorisation holders in the EEA are included in the service.
- They are grouped as follows:
  - Substances by active moiety including e.g. salts, esters as well as combinations.
  - Herbal substances by genus including combinations.
- The total number of all substance groups included in the literature-monitoring service is based on the Agency's allocated budget.

Significance of Literature Search

- Literature searching is an important activity in Pharmacovigilance and is useful to identify rare and very rare adverse reactions associated with the medicinal products.

- Literature search also aids the MAH in the following key functions:
  - Regulatory Reporting of ICSRs
  - Safety Surveillance

Literature search thus is a significant source of information for the monitoring of the safety profile and of the risk-benefit balance of medicinal products, particularly in relation to the detection of new safety signals or emerging safety issues

Questions?