Module 5 – Literature Search

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1. Introduction to Literature Search

Although spontaneous reporting is an important source of information about new Adverse Drug Reactions (ADRs), many times 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 adverse reaction case reports (also referred to as individual case safety reports (ICSRs)). Published case report are considered as an important source of information as these are usually about serious, unexpected ADRs, prepared by physicians (thus, medically confirmed reports) who have strong suspicion about causal role of the medicinal product and are usually detailed enough to include all information relevant for adequate assessment for example past history, concomitant medication etc. Many times authors also publish case series, i.e. publications with information about multiple patients with similar adverse reactions.
- 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

Pharmaceutical companies/marketing authorization Holders (MAH) need to screen scientific literature and triage for adverse events (AEs) related to the products so that they can be promptly reported for regulatory compliance through a systematic literature review of widely used reference databases (e.g. Medline, Excerpta Medica or Embase), no less frequently than once a week. Peer reviewed and indexed medical and scientific journals are the primary source if high quality information about new ADRs.

Literature screening is mandatory to address the legal requirements per European Medicines Agency and Food and Drug Administration regulations.

In France, it is the responsibility of the editors to check with the authors of case reports to ensure that the case has been reported to one of the Regional Pharmacovigilance Centre. Only cases that have been already reported to a Regional Pharmacovigilance centre are accepted for publication. As the editors of all medical journals don't require authors to inform

regulatory authorities and manufacturers prior to sending the case reports for publications, therefore ,it becomes all the more important for MAHs to regularly screen worldwide literature for information about safety issues related to the products marketed by them.

Many times relevant information may also appear either exclusively or much earlier in local journals therefore, pharmaceutical companies are also required to regularly scan some important journals published in local languages in countries where the company is marketing its products. In addition to searching local literature, pharmaceutical companies should also appropriately process the information published on internet or appearing in general magazines (i.e. magazines that are not medical or scientific). For worldwide and local searching, MAHs are expected to regularly scan the literature in a defined manner. At present, there is no such regulation defining the need to search in internet or other media.

However, MAHs are expected to periodically scan their own websites. Therefore, MAHs should have well drafted Standard Operating Procedures (SOPs) covering frequency of literature searching, databases to be searched, strategy for literature searching review of literature hits, documentation and criteria for expedited reporting from literature searching.

These aspects of literature searching have been discussed in detail in this chapter.

2. Methodology of Literature Search

2.1 Database to be searched

It is responsibility of the MAH to ensure that the database searched for literature searching should have a wide coverage else some relevant hits may not be captured; this can be a potential inspection finding. Some of the databases widely used by pharma companies for literature searching include Medline and Embase.

Embase, it is a privately held database by Elsevier. It covers some 8500 journals including all MEDLINE journals.

Journals covered by EBSCO, a private US Company (which also includes MEDLINE with full text), International Pharmaceutical Abstracts covering 800 journals and The Allied and the Complementary Medicine Database. These sources cover Medical Subject Headings (MeSH).

SEDBASE is a database derived from Meyler's Side Effects of Drugs and contains cynopses of relevant ADRs as well as drug interactions. Some other multidisciplinary databases covering various scientific and biological journals are Scisearch, Biosis Previews and Derwent Drug File. As the name itself indicates, CANCERLIT and AIDSLINE are databases specific to cancer and AIDS respectively.

TOXLINE database covers the toxicological, pharmacological, biochemical and physiological side effects of drugs and other chemicals. CIOMS V recommends that MAHs should use at least two different databases to ensure maximum coverage.

2.2 Frequency of literature searching

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.

2.3 List of Products

The SOP should indicate the list of the products for which literature searching is done. It includes all approved products. Regular literature searching is also required for products that are under the approval process. This will ensure that companies are aware of the changes if any, in the benefit risk profile of the product and can promptly share this information with regulators. In fact not carrying out literature searching for products under the approval process is a common finding from the Pharmacovigilance inspections conducted by MHRA.

Further, literature searching should be carried out both for active substances as well as brands. Not conducting literature searching for brands is also a common inspection finding.

2.4 Criteria for literature searching

The key words for literature searching should not be limited to adverse events or adverse drug reactions, in fact pharmaceutical companies should also include terms like overdose, drug abuse, dependence, pregnancy, lactation, lack of efficacy, contraindications, drug interactions, food-drug interactions to ensure that all publications relevant for safe administration of a medicinal product are duly captured. Similarly literature searching should also include terms like fatal and death to ensure that cases reporting mortality are captured it also equally important to capture cases where overdose dose not result in any adverse reactions or normal fetal development and delivery subsequent to exposure during pregnancy.

2.5 Limits for literature searching

The purpose of using limits in literature searching is to avoid capturing of irrelevant hits thereby, increasing the specificity of literature searching. Limits should be applied considering the regulatory requirements. Life cycle of the product and the short comings and characteristics of the database, for example it may be acceptable to use limits “human” for off patented generic drugs that are in market for several decades whereas the same may not be acceptable for medicinal products that have recently been published. There should be no language limits and articles published in other languages should be translated for processing. Results / History should be documented in a way that limits used for search strategy are clearly evident.

2.6 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. Although, articles published in English are acceptable in many countries, some countries like Japan request that articles should be submitted only after these have been translated in Japanese. Therefore, companies should assess the requirements for translation as per the countries where the product is marketed. In many countries there are service providers who translate the world wide literature as well as safety alerts published by regulatory authorities like FDA, MHRA and circulate the same to MAHs who subscribe to such services. This saves duplication of efforts as all the MAHs are not

required to individually translate the articles. Such a collaborative effort can result in considerable cost saving for generic companies.

2.7 Review of hits

Literature hits 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. Drug review, drug class reviews and meta-analyses must be evaluated thoroughly to identify information regarding new adverse reactions, drug interactions, contraindications, abuse, misuse etc. All new information collected form publications must be reviewed in detail at the time of conducting routine benefit risk analysis as well as the time of preparing PSURs. All published studies are included in the section 7.3 of PSURs, 'Published Safety Studies". Initial Receipt Data (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. Thus, if abstract contains minimum information for the case to be valid, then IRD is taken as the data search was conducted. Thus, MAH is expected to process the case with abstract. Although, some people may argue that cases reported in literature may have occurred long before the publication and therefore, it is not appropriate to expedite such cases with abstract only, rather one should wait for the procurement of full article. However, as per the regulatory requirements, all publications with information about unexpected, adverse reactions should be shared with regulatory authorities at the earliest possible.

Nowadays, library services are quite efficient; therefore, usually it is possible to procure full articles in one working day. Thus, it is advisable that rather than processing the case from abstract, MAH should attempt to procure the full article if possible without delaying the timelines for expedited reporting (which is usually 15 days). Full publications need to be submitted with all expedited reports. Again, timelines for expedited reporting should not be compromised if for any reason there is delay in procuring the full publication. Let us consider the example of a publication in different language with abstract in English and the minimum information is available in the abstract. In such cases, procurement followed by translation of the publication may itself take a few working days and it may itself take a few working days and it may not be thus possible to wait for the full publication and process the case in 15 days. Therefore, in such circumstances, the case should be processed with the abstract and abstract

should be submitted long with the expedited reports followed by procurement of the complete publication. A follow-up report should be submitted after processing the case with full publication.

It should be noted that like spontaneous cases, IRD is the day when any staff from the company, its subsidiaries are outsourced companies working on behalf of MAH become aware of the publication.

Literature articles for expedite reporting to health authorities are ICSRs (solicited/ unsolicited), describes ADRs and other safety information. Usually the frequency for literature search is once a week. Literature search strategy to identify ICSRs includes:

1. **<u>What articles to look for</u>**:
    - Adverse drug reactions
    - Overdose
    - Lack of efficacy
    - Drug exposure via parent
    - Drug misuse
    - Drug abuse
    - Unintended beneficial effects

    In the literature search strategy these are requested via several "key words" (i.e., overdose, toxicity)
2. Publications for aggregate safety reports includes published studies with new or relevant safety findings (positive or negative), and published studies in special populations. The usual frequency for literature search is once a month. Literature articles important for aggregate safety reports are:
    - Meaningful safety information that adds or brings specificity to existing safety profile;
    - Literature articles describing safety information in special population not previously mentioned in reference documents;
    - Published study performed for safety issue with company's product regardless of result;

- Any literature article describing a safety topic where company's performing cumulative overview in PSUR for safety topic that may be a signal or a potential signal regardless of conclusion;
- Important non-clinical safety findings;

3. Literature search for signal detection activities are usually done on a monthly basis (however, frequency may change product life-cycle)
4. Literature authors should assess the event related to company's product or product with same INN.
5. As per European Union requirement, search for medical and scientific literature must be done at least three international databases.

GUIDELINES FOR LITERATURE ICSRS

- For 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

OR

- 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

OR

- Literature article should have information regarding product 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

**Indicate in report that product source and/or invented name not identified

Reaction/Event

- As topic of article, author suspects relationship between event and product
- Any adverse event mentioned in history does not qualify for reporting from literature

Selection criteria for Valid ICSRs

Each valid ICSR has its own case in company's safety database:

- Unsolicited cases
    - All entered
- Solicited cases
    - Only entered if report causality is associated

Source	**Seriousness**	**Company's product**	**Entered in safety database**
Unsolicited	Serious and non-serious	Yes, No or unknown*	Yes
Solicited	Serious associated	Yes or unknown	Yes
Solicited	Serious associated	No	No
Solicited	Non-serious	Yes, No or	No

		unknown	

*Unknown means that it may be or may not be a company's product

<u>If multiple patients are mentioned in the literature abstract/article</u>

If identifiable patients:

- Create separate cases in safety database
- Cross-reference cases (Case Details tab/Related Cases tab and in narrative)

If do not have identifiable patients, but meet selection criteria:

- Create one case in safety database
- Patient number on Case Details tab entered as appropriate: "02" if two patients in the article
- If follow-up received identifying the patients, additional cases created in safety database and cases are cross-referenced (Case Details tab/Related Cases tab and in narrative)
- Regulatory reporting based on seriousness and listedness of reported adverse events

<u>Special situations</u>

The following are entered in company's safety database:

- **Poison Control Center Annual reports**
    - Only ICSR description
    - List of adverse reaction with no details are not valid case
- **Serious ICSRs from License-In Partners**
- **Retrospective Studies**
    - Only entered if all the criteria for valid ICSR is met
- **Publications with unexpected therapeutic effect**
- **Courtesy cases**

The following are NOT entered in company's safety database:

- ✓ Review articles without valid ICSR information not entered, but may be mentioned in the literature section of the PSUR/PBRER
- ✓ Tabulations published by Health Authorities or equivalent, such as World Health Organization
    - May be mentioned in literature section of the PSUR
- ✓ Efficacy studies including safety data with no case reports

Entered in company's safety database, but not as a "literature" ICSR:

- ✓ Reports from unpublished scientific papers and abstracts submitted, but not accepted for presentation or publication
- ✓ Lay publications

Contact dates:

- First contact date (Day '0') is date when literature article/abstract was detected in the literature search database by an employee of company or any person acting on behalf of company with background/training to identify/confirm valid ICSR
- If article/abstract requires translation into English, the translation is considered follow-up information
    - ➢ The date the translated article is received is considered the last contact date (company contact date) and new clock start date is applied

Follow-up information

- All requests for follow-up information from the reporter are made through the affiliate's PV head or deputized person of the country of the author
- Most aggressive follow-ups are directed at valid ICSRs of serious, unlisted adverse events that lack details important for assessment of the case
- Copy of the article should accompany request to an affiliate's PV head or deputized person for follow-up (if affiliate's PV head or deputized person did not report article to PV office or delegate)

2.8 Documentation

MAH should maintain records of conducting literature searches including history as an evidence of routinely conducting literature searching as per the regulatory requirements. This becomes particularly significant if there are no relevant publications. Results/history should be maintained in such manner that limits used for search strategy are clearly evident.

2.9 Literature reports as Anonymized Single Patient Reports

MHRA process the case reports from literature and shares the literature case reports as Anonymised Single Patient Reports (ASPRs) with companies marketing the active substance. These need to be processed in a similar manner as other literature articles. Earlier in the last decade, under BROMI initiative MHRA has stopped sending ASPRs from literature articles.

2.10 Follow-up of literature articles

Generally literature reports are detailed and contain enough information for appropriate assessment. However, follow-up may be required with the author if details important for assessment of a case are missing especially from serious, unexpected cases, follow-up with authors of literature articles is usually challenging and unlikely to provide further information because –

- Authors generally take sufficient time to prepare case reports and in all likelihood would have included all information available with them.

By the time, a case appears in published literature sufficient time would have elapsed since the occurrence of the event since the occurrence of the event and medical record would have been archived since then.

2.11 Challenges in literature searching

One of the key challenges in literature searching is to ensure that the strategy used for searching is robust enough to capture all relevant hits. MAHs use different types of strategies to ensure complete coverage of publications. These strategies complement each other, for example weekly literature searching, cumulative searching and auto-alerts.

Knowledge of the processes used in database is also critical for appropriate and efficient literature searching and include the timelines to upload the published articles, lag period between uploading the articles and adding key words, updating the Medical Subject Heading (MeSH) terms etc. Some databases upload the published articles much before keywords are

added. Under such circumstances, literature searching may not get the desired results even when MAH is using correct strategy. These issues can be resolved by knowing the lag period between uploading the article and adding the keywords and updating the literature strategy accordingly. Some other solutions include supplementing the weekly searches by auto-alerts and additional searches with longer time intervals for example monthly literature searching.

Another common challenge of literature searching is duplicates, which may be because:

- Authors may have reports the case to MAH or the regulatory authority prior to publishing.
- Authors may have first published the single case report followed by the publication of case series.
- Authors may have presented the case in conferences (and thus the case was published as the proceedings of the conference followed by the publication in a peer reviewed journal)
- Authors may have published the case in local journals followed by publication in a peer reviewed journal
- Drug safety reviews my cross refers to the publications of individual cases or some case may have been indexed in many databases in a slightly different manner.

Further, many of the ASPRs shared by MHRA are form the literature reports which may have been captured by MAH independently during their routine searches. Recently, under BROMI initiative MHRA has stopped sending ASPRs from literature articles.

Therefore, on receipt of a literature case, drug safety terms should carefully search for the duplicates. Besides the reported term and patient identifiers, duplicate searching should also be done using name of the author and the country of incidence.

Another challenge of literature searching is the availability of incomplete information and poor response from authors on follow-up. Therefore, there have been attempts to set the guidelines for defining the contents of case reports so as to ensure that high quality reports with complete information are published.

3. Monitoring of Medical Literature (MLM)

The European Medicines Agency (EMA) is responsible for monitoring a number of substances and selected medical literature to identify suspected adverse reactions with medicines authorized in the European Union, and for entering the relevant information into the EudraVigilance database.

The service is fully operational as of 1 September 2015.

Scientific and medical literature is an important source of information to identify suspected adverse reactions with medicines authorised in the European Economic Area (EEA).

In line with the guidance in Good Pharmacovigilance Practices (GVP) Module VI, marketing authorisation holders are required to monitor medical literature and to report individual cases of suspected adverse reactions for medicines for which they hold a marketing authorisation in the EEA. This has led to duplication of efforts by marketing-authorisation holders for active substances included in more than one medicine, and duplication of reports entered into EudraVigilance and national safety databases.

The monitoring of medical literature and the entry of relevant information into

- EudraVigilance will be carried out by EMA in order to:
- Enhance the efficiency of adverse reactions reporting;
- Provide a simplification for the pharmaceutical industry;
- Improve data quality by reducing the number of duplicates;
- Contribute to resource savings for the pharmaceutical industry;

Support signal detection activities by national competent authorities and marketing authorisation holders.

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.

The lists of substance (mainly chemical) and herbal-substance groups which are subject to the monitoring activities by the Agency are published in a separate document.

The total number of all substance groups included in the medical literature monitoring service is based on the Agency's allocated budget for these activities and will be subject to annual review.

More than 3,500 marketing-authorisation holders in the EEA for the substance groups benefit from the service, and more than 640 marketing-authorisation holders for the herbal substance groups.

The medical literature covered by the medical literature monitoring service has been designated in line with GVP Module VI, and is based on the use of literature reference databases by the Agency's contractor as outlined in the below document:

4. Significance of Literature Search

Literature searching is an important activity in Pharmacovigilance and is quite useful to identify rare and very rare adverse reactions associated with the medicinal products. During Pharmacovigilance inspections, inspectors, spend considerable time to understand the processes followed by the company and receipt and processing of literature hits. Apparently a simple process, methodological literature searching is critical to ensure that all relevant hits are captured, processed and reported as required. Therefore, companies should have adequate SOPs to define the processes for literature searching including databases to be searched, strategy and frequency of literature searching. Process should also be defined for local literature searching, duplicate searching, follow-up with authors and expedited reporting of ICSRs captured from literature searching.

Regulatory Reporting of ICSRs

MAH is expected to expedite reporting of the serious and unexpected cases within 15 days, if they are not able to exclude their product. All literature hits however, are reported in the PSURs. MAH can exclude their product if some other brand name is mentioned, the formulation and the dosage form mentioned in the literature report is not marketed by the MAH or MAH is not marketing the product in that particular country from where the case is reported.

As generic drugs are simultaneously marketed by many companies, all these companies are simultaneously conducting the literature searching and reporting the serious unexpected cases on an expedited basis. This in turn means that regulators are receiving the same case from multiple sources, which increases the amount of work at regulatory authorities to process the expedited reports from literature. To resolve this issue, MHRA on its website has published a list of all literature articles that have been received by MHRA and the authority is regularly updating this list. All companies are required to cross check this list prior to expediting a literature case report to MHRA. The case reports already appearing in that list need not be expedited to MHRA by other companies.

Safety Surveillance

Literature review is the corner stone when performing routine safety surveillance activities such as Aggregate reporting, signal detection, response to ad-doc regulatory queries.

The process involved is the same just that the frequency, search criteria and the outcome of the literature search would be different from routine literature search activity.

5. Guide to Further Reading

a. PubMed online training. Pubmed Toturials. Available on website

http://www.nlm.nih.gov/bsd/disted/pubmed.html

b. Monitoring of medical literature and entry of adverse reaction reports into EudraVigilance

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000633.jsp&mid=WC0b01ac05808ce84c