The Importance of Literature Searches in a Regulatory Environment

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In recent years, regulatory authorities have adopted more stringent safety regulations pertaining to marketed products. The medical literature is a key source of safety information about these products, as new types of adverse reactions may first come to light as published individual case reports or a part of published clinical studies.

The medical literature is defined as published abstracts or articles in medical/scientific journals, and unpublished manuscripts involving case reports, important safety findings or clinical studies including posters, letters to the editors, and associated communication from scientific meetings. Regularly scheduled, well-structured searches of the medical literature are conducted to capture this information. Marketing Authorization Holders (MAHs) must fully utilize this information to fulfill regulatory obligations while also staying current on the risk/benefit profile of their product.

WHAT ARE THE REGULATORY OBLIGATIONS?

The FDA requires that reports of serious, unexpected adverse events be submitted (via MedWatch) for products that have the same active moiety as that of the MAH. In their Draft Guidance for Industry, the FDA states that "[t]his is true even if the excipient, dosage forms, strengths, routes of administration and indications vary". For example, even though a company markets only an oral ibuprofen formulation, they must submit reports for events involving intravenous ibuprofen. Additionally, the FDA requires that when a serious, unexpected adverse event has been published in a foreign language, the MAH should translate the publication into English promptly.

WHAT ABOUT PRODUCTS MARKETED OUTSIDE THE US?

For MAHs with products marketed in the EU, the MAHs are "expected to maintain awareness of possible publications by accessing a widely used systematic literature review and reference database no less frequently than once a week". The search frequency is not as often for MAHs with products in the US; searches should occur no less frequently than monthly. Other regulatory agencies may have varying requirements around search frequency. Unlike in the US, MAHs in the EU must report more events—both serious and non-serious, expected and unexpected.

HOW DO YOU STRUCTURE THESE REPORTS?

The structuring of these searches and the subsequent review of search results may prove challenging to some MAHs. It is expected that MAHs will search at least two conventionally recognized databases, such as Medline and Embase. Searches are structured to be as broad as possible to minimize any chance of missing a relevant citation. Typically, the generic and trade name (if applicable) of the product are searched,

without any additional terms such as “adverse event” which would restrict results and increase the likelihood of a missed citation.

Searches on a given product may yield hundreds of articles, yet only a fraction of these may contain valid cases. Carefully screening these search results for potential minimum safety information (MSI) is imperative.

If it appears an abstract has MSI, the full text of the article is then retrieved. The article is then thoroughly reviewed and subsequently reported if an identifiable patient is described, a valid event has occurred, and a suspect product (as defined by the authors) is marketed by the MAH conducting the search.

THE SAME RULES APPLY TO GENERIC DRUGS

All of these requirements apply to both branded and generic drug manufacturers alike. Older products that are manufactured by many companies will generate many reports to the FDA from the same article. For example, an article that describes the case of a patient using high doses of metformin to commit suicide will generate multiple expedited reports—all from MAHs that market metformin. However, if a branded form of metformin (Glucophage or Fortamet) is mentioned in the article as being suspect, then only the MAH that distributes that particular product is required to report. MAHs can query the author to clarify the brand/source of the suspect product. Without further information, however, the MAH should assume it was the company’s product.

CHALLENGES

There are numerous other challenges that arise during the literature review process. Each article represents an opinion or observation of the author, and is not necessarily confirmed or proven causality. Similarly, articles have a wide variation in quality and completeness, especially surrounding concurrent medications, event outcome, and seriousness. Multiple drug products may be mentioned in the text, without any definitive attribution by the author. Adverse drug reactions may be confounded by the patient’s underlying disease state, which may not be available. For example, oncology patients are typically on multiple therapies, and it can be unclear if events that occur during therapy are due to a drug therapy (which one?), the patient’s cancer or some other pre-existing medical condition. Therefore, the individual reviewing full text articles needs to have the necessary medical knowledge to digest the information presented by the author, and be able to accurately and quickly assess the case.

Cost and manpower pose additional challenges. Subscription access to databases such as Embase runs tens of thousands annually. While some literature articles can be located from free sites, most typically cost between $20-100. Factor in the cost of translations for certain articles (up to $600 depending on the length of the article and language involved), one can see that literature review can be an expensive proposition before the first case is even processed. There is often a wealth of data in literature articles, with extensive laboratory values and detailed information on the clinical course of events. As a result, processing literature cases is very time consuming and a MAH must have sufficient manpower to properly database these cases.

In many cases, the authors discuss other reported cases in the literature that may be similar to the case at hand. The list of references within literature articles may provide additional, valuable safety information about a particular adverse reaction. But evaluating these citations can be time consuming. Assuming prior literature searches by a MAH have been thorough, all previously published case reports should have been captured. However, it is recommended that MAHs have a procedure in place to review references (i.e.,

cited case reports published in the last five years). MAHs can then compare these references with databased cases to ensure that all relevant cases have been captured to report to regulatory authorities.

Like all other safety reports, there tends to be under-reporting. Conversely, for certain "hot" safety issues, there may be increased reporting due to increased attention. Regardless of the quality and completeness of the article, MAHs must utilize the information contained within the text and report to the proper authorities as necessary.

Although literature is key source of safety information, there are numerous challenges in conducting searches, sifting through and reviewing search results, as well as in the subsequent regulatory reporting. MAHs must be intimately familiar with the regulatory requirements surrounding literature to fulfill their regulatory obligations and maintain up to date knowledge on the safety profile of their product.

NOTES

For additional information:

1. FDA Draft Guidance for Industry: Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines (http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074850.htm)
2. EMA Guideline on good pharmacovigilance practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129135.pdf)
3. CIOMS V: Current Challenges in Pharmacovigilance: A Pragmatic Approach (http://www.cioms.ch/index.php/component/booklibrary/?task=mdownload&id=47)

ABOUT THE AUTHOR

Thomas Winkler, PharmD, joined Drug Safety Alliance, Inc. in 2012. He manages literature services for DSA | Ashfield Pharmacovigilance, including all scheduled and ad hoc searches. He is responsible for handling escalated medical information requests. He also serves as a preceptor for 4th year pharmacy students from the University of North Carolina Eshelman School of Pharmacy.

ABOUT US

Founded in 2000 and acquired by UDG Healthcare in 2012, as part of its Ashfield Division, Drug Safety Alliance, Inc. (DSA) is a global leader in safety and risk management services supporting pharmaceutical, biotech, medical device, consumer health and animal health organizations. Uniquely focused on pharmacovigilance, DSA provides comprehensive outsourced solutions and modified services to augment existing safety departments. In addition to pharmacovigilance Ashfield offers numerous services in areas including commercial, clinical, healthcare communication, insight and performance, market access, medical information, as well as meetings and events. DSA is headquartered in Research Triangle Park, North Carolina. For more information, please visit www.DrugSafetyAlliance.com.

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