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Pharmacovigilance White Paper

Understanding Safety Surveillance

Pharmaceutical companies have ethical and regulatory responsibilities to collect, analyze, and communicate information about the safety of their medicines. These responsibilities begin in a drug's research and development and continue throughout the drug's lifespan.

Safety in Clinical Studies

Pre-approval clinical studies are conducted to evaluate the safety and efficacy of a new medicine. Phase I studies are structured to test the safety of an investigational compound in small numbers of subjects. The outcomes of these studies are used to help design and determine dosing in later studies. All of the information that is known about a drug's safety profile is included in the Investigator Brochure that is provided to clinical investigators. Any events that occur that are not included in the Investigator Brochure are classified as "unexpected." Any events that are fatal, life-threatening, require inpatient hospitalization, result in significant or persistent disability or incapacity, or result in congenital anomalies are considered serious adverse events (SAEs). If a sponsor believes that an unexpected, serious adverse event is causally related to the study medicine, the sponsor is required to report the "Suspected Unexpected Serious Adverse Reaction" (SUSAR) to regulatory authorities on an expedited basis. Within 7 days of becoming aware of any fatal or life-threatening event, a sponsor must report the event to regulatory authorities. Additional follow-up information on the patient's status must be provided in 15 days.

Whenever a potential new serious risk is discovered, the study sponsor is required to notify investigators. Either the sponsor or the investigators will inform the independent ethics committees overseeing the study, who in turn will determine how this information is to be communicated to patients. Patients may be asked to renew their informed consent to participation in the study following receipt of this new information.

Postmarketing Surveillance

While the most commonly occurring side effects can be identified during pre-approval clinical studies, rare adverse events, as well as those with long latency periods, may not be detected until after a medicine is approved for widespread distribution. Unsolicited, "spontaneous" reports may be received from healthcare providers or other caregivers, patients, lawyers, the media, or regulatory authorities, among other sources. Any events that are not listed in the medicine's label (*i.e.* the Prescribing Information or Summary of Product Characteristics) are classified as unexpected. All spontaneously reported serious adverse events must be reported to

regulatory authorities within 15 days, regardless of believed causation. The 15 day reporting timeframe begins whenever any person in the company, or a person working on behalf of the company, becomes aware of the event. The manufacturer is subsequently expected to report any significant follow-up information it learns about the case. At periodic intervals, the manufacturer is required to submit aggregate reports of all safety data collected on the medicine.

In most pharmaceutical companies, as soon as a report of a possible adverse event is received, the information is entered into a safety database. Physicians, scientists, and other professionals in the company's medical safety department review each case and determine whether expedited or regular, periodic reporting is required. Additional information may be requested to better understand the circumstances surrounding a particular case. The medical safety department professionals also determine whether, as a result of the new information, changes to the medicine's label are necessary.

Whereas only a few years ago, most safety data was reported to regulatory authorities using paper forms, today most reporting is conducted electronically. Electronic reporting has the advantage of allowing simultaneous transmission of safety data to multiple regulatory agencies around the world.

Analyzing Safety Data

Information that has been entered into a company's safety database undergoes both qualitative and quantitative analyses by medical safety department professionals to identify possible safety signals. Qualitative analysis involves an examination of the circumstances leading to an adverse event to identify a possible causal link. Quantitative analysis involves using statistics to determine whether certain adverse events are occurring with a greater frequency than previously expected. Both qualitative and quantitative analyses are necessary to identify and evaluate possible safety signals. Often, however, it is not possible to fully evaluate a possible safety signal using spontaneous report data alone. Further investigation of possible safety signals may involve re-examination of previously collected clinical study data to determine whether such signals were present during clinical trials, undertaking new clinical studies designed to produce information concerning the possible signal, or conducting observational/pharmacoepidemiologic studies.

Confidentiality of Safety Data

A number of technical and organizational controls typically protect pharmacovigilance data from unauthorized access, use, alteration, loss, disclosure or other processing. It is standard practice for pharmaceutical companies to have separate groups within their organization that are responsible for pharmacovigilance, as well as separate files and databases to support these activities. The employees of the

company who are responsible for pharmacovigilance activities are bound by obligations of confidentiality covered by the company's employment contracts, policies, or standard operating procedures. Even within a pharmacovigilance group, confidential information learned in the course of such activities is shared only as necessary to conduct activities such as statistical analyses and regulatory reporting. In all cases, these activities are subject to rigorous controls and inspection by health regulators. These regulatory controls require that (i) access to systems containing pharmacovigilance data be restricted to those who require it in order to perform job functions; (ii) audit trails be maintained that track all database changes; and (iii) systems undergo validation to ensure accuracy, reliability, and consistent intended performance.

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