

Role of IT in Managing Adverse Drug Events

Clinical data determines the birth, existence, and unfortunately at times even the demise (due to adverse events overshadowing risk benefit ratio) of a pharmaceutical drug. Regulatory agencies like US FDA, MHRA, MHLW or EMEA etc. approve a new drug based on the stringent evaluation of pre-clinical and clinical trial data (Phases I to III), drug safety monitoring data along with other stipulated pharmaceutical information submitted by the sponsor (Pharmaceutical Company). However, getting a marketing authorization approval from the regulatory agency does not mean that the drug would be off the scanners of the regulators. This is because, till then the drug has been tested only on a small and defined human population undergoing clinical trials. Once the drug is marketed it is consumed by larger and diverse population including those with possible co-morbid conditions and those who may be on concomitant medication. Hence, it is possible that certain adverse drug reactions previously unknown may become apparent and those known may show a change in their incidence. Regulatory agencies require pharmaceutical manufacturers to carry out post-marketing pharmacovigilance to monitor previously known or unknown adverse drug reactions as part of post-marketing pharmacovigilance efforts.

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Abbreviations

ADR	Adverse Drug Reaction
AERS	Adverse Event Reporting System
EMA	European Medicine Evaluation Agency
ESTRI	Electronic Standards (for the) Transmission (of) Regulatory Information
EU	European Union
ICSR	Individual Case Safety Report
MedDRA	Medical Dictionary for Regulatory Activities
PSUR	Periodic Safety Update Reporting
PV	Pharmacovigilance
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
UMC	Uppsala Monitoring Center
US FDA	United States Food and Drug Administration
VAERS	Vaccine Adverse Event Reporting System
WHO	World Health Organization

Introduction

It is an accepted fact that despite the best of research and development, no drug is free from adverse drug reactions. It is due to this, that the regulatory agencies take into consideration the risk - benefits of a drug before granting a marketing authorization. To minimize risk, regulatory authorities insist on rigorous testing before the drug is approved and also mandate the pharmaceutical companies to monitor the drugs for any adverse events once the drug reaches the market. Phase-IV of clinical testing of a drug involves the assessment of the risk – benefit ratio of approved drugs that are being consumed by larger population. Pharmaceutical companies also report adverse events to national centers of member countries which in turn updates the AERS database at Uppsala monitoring center of WHO.

History

It was not until the disaster caused by thalidomide in 1961, that the first systematic international efforts were initiated to address drug safety issues. This led to the creation of WHO Pilot Research Project for International Drug Monitoring in 1968. The intention behind the pilot program was to ultimately develop a system applicable internationally to monitor previously known or unknown adverse drug reactions. A concept paper subsequently followed and all these led to the practice and science of pharmacovigilance. Systems were developed in Member States for the collection of individual ADRs and their evaluation. The collection of international ADR reports in a central database, would serve the important function of contributing to the work of national drug regulatory authorities, improve the safety profile of medicines, and help avoid further disasters.

Safety Monitoring through the life-cycle of a drug

The safety process involves the use of data for decision making, but the type of data collected and the way it is managed, analyzed and used is important to accommodate each specific step in the drug development cycle. Figure–1 is a diagrammatic representation of the pharmacovigilance process through the lifecycle of a drug, carried out by the manufacturers based on the regulatory recommendations.

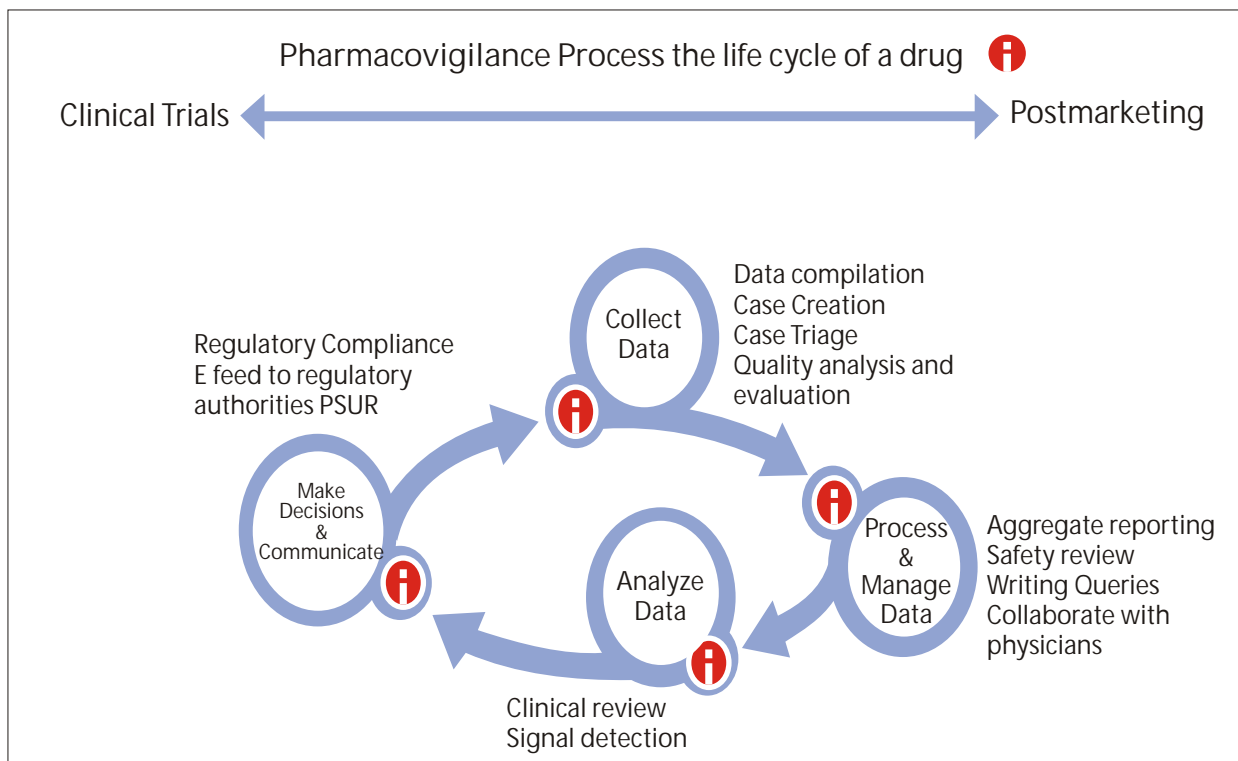


Fig 1: Pharmacovigilance Process the life cycle of a drug

Pharmacovigilance and WHO

WHO defines pharmacovigilance as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems. It is carried out by pharmaceutical companies on their products and by government agencies on all medicinal products. Figure-2 provides flow of pharmacovigilance information monitored by WHO.

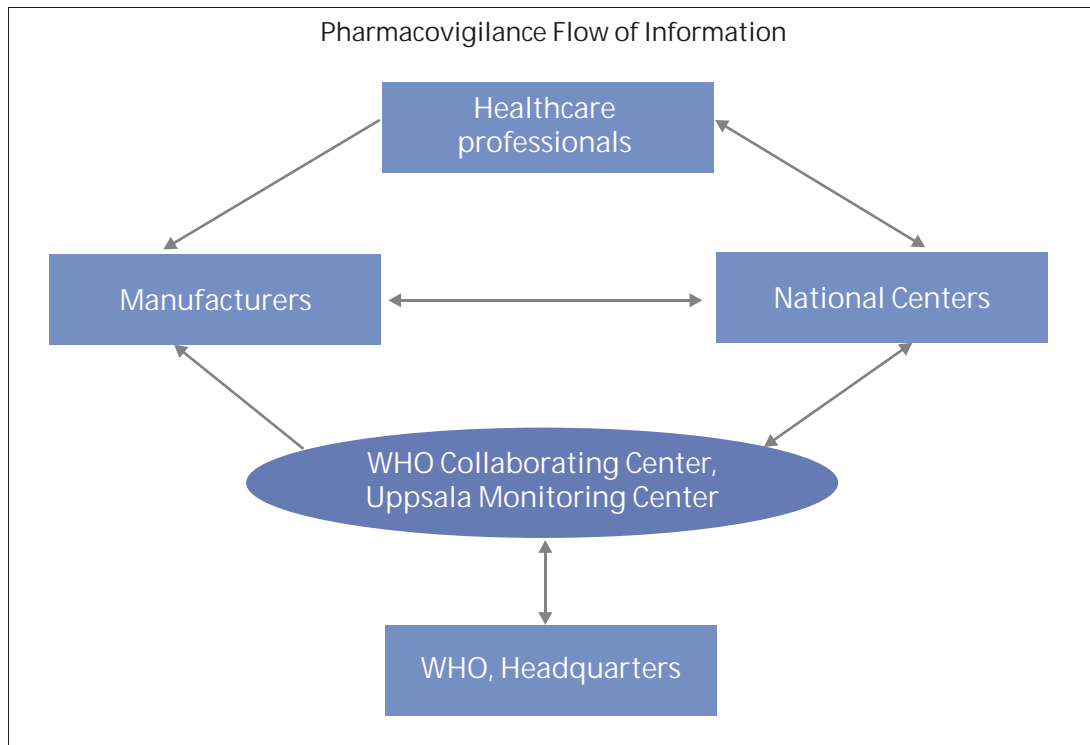


Fig 2: Pharmacovigilance Flow of Information

The Uppsala Monitoring Centre

The WHO Programme for International Drug Monitoring is co-ordinated by the Uppsala Monitoring Centre (UMC) in Uppsala, Sweden, with oversight by an international board. The Programme has expanded to include more than eighty one member countries, as on 2006. The principal function of the Uppsala Monitoring Centre is to manage the international database of ADR reports received from National Centres. As on Sep 2006 this database held nearly 3.7 million case reports. The majority of national contributing centres have easy electronic access to these. The UMC has established standardized reporting of all National Centres and has facilitated communication between countries to promote rapid identification of signals.

Key Drivers For Pharmacovigilance

Regulatory mandates

21 CFR parts 310, 312, 314, 320, 600, 601, 606 of the US FDA mandates the pharmaceutical companies to conduct post-marketing surveillance and report ADRs within stipulated time-frames. Similarly regulatory agencies of various other countries also mandate all pharmaceutical manufacturers to conduct adverse drug event monitoring of approved drugs.

Typically, the pharmaceutical companies are mandated to submit post-marketing data periodically. Any serious/unexpected adverse event occurring in the patients has to be reported within a stipulated time-frame of 7 to 15 days from the occurrence of the event to the regulators. The regulatory agencies based on the incidence and seriousness of the adverse drug reactions evaluate the risk benefit ratio and then provide appropriate recommendations such as warning insert, change in labeling or even withdrawal of the drug from the market. There have been many instances of pharmaceutical companies getting into litigation quagmire with drugs that have caused serious adverse events (Refer box for "as the cookie crumbles")

As the Cookie Crumbles

Pharmaceutical companies spend millions of dollars on R&D and new drug development. It is estimated that almost 15-16% of the sales of drugs are spent on the drug development even before the drug is launched; it has also been observed that comparatively only a minuscule percentage of the sales is spent on pharmacovigilance activity post-marketing approval. Some pharmaceutical companies have learnt the hard way that inadequate adverse event monitoring can bring devastating damages financially, to the brand image of the company and more importantly to the innocent patients who consume the drugs. Given below are some examples of blockbuster drugs that have made headlines due to their serious adverse effects:

- Rosuvastatin - US FDA has revised label to highlight information on the safe use of the drug to reduce the risk for serious muscle toxicity (myopathy/rhabdomyolysis).
- Cerivastatin - Sometimes causes fatal Rhabdomyolysis and has been withdrawn from the market.
- Paroxetine - Causes suicidal tendency, addiction and severe withdrawal symptoms.
- Rosiglitazone - Has been found to increase risk of heart attack and increased chances of cardiac death. US FDA has issued safety alert for the drug.
- Rofecoxib - Causes cardiac problems and has been withdrawn from the market.
- Fenfluramine - Causes cardiac problems and was withdrawn in 1997.

Brief Overview of Pharmacovigilance Process Recommended by US FDA

Good pharmacovigilance is based on collection of data from adverse event reports also known as case reports. As acknowledged by the FDA, it is very difficult to arrive at a conclusion whether the event was the outcome of the pharmaceutical product. FDA recommends sponsors to search for similar or related cases from the global adverse database (UMC) or other available sources such as FDA AERS or VAERS etc.

When a situation arises wherein one or more cases suggest a safety signal warranting additional investigation, the FDA recommends a case series to be assembled and clinical information to be summarized to characterize the potential safety risk and identify the risk factors. Case series are usually developed based on the information provided on the adverse reports.

The FDA encourages the use of statistical and mathematical models (Data Mining). Data mining techniques can provide additional information related to the existence of an excess of adverse events reported for a product.

Pharmacovigilance plan

A pharmacovigilance plan is developed by a sponsor that is focused on detecting new safety risks and/or evaluating already identified safety risks. Specifically, a pharmacovigilance plan describes pharmacovigilance efforts above and beyond routine post-marketing spontaneous reporting, and is designed to enhance and expedite the sponsor's acquisition of safety information.

PV in EMEA and EudraVigilance

The VOLUME 9A of the Rules Governing Medicinal Products in the European Union has laid guidelines on Pharmacovigilance for Medicinal Products for Human Use and it requires the marketing authorization holder to ensure that he has an appropriate system of pharmacovigilance in place in order to assume responsibility and liability for his products on the market and to ensure that appropriate action may be taken when necessary. The Marketing Authorisation Holder should therefore ensure that all information relevant to the risk-benefit balance of a medicinal product is reported to the Competent Authorities and the Agency fully and promptly in accordance with the legislation.

EudraVigilance

For European medicines, the EMEA collects all ADR's and SUSAR's reports within a central database called EudraVigilance. EudraVigilance is a central computer database created by the EMEA in December 2001. It contains adverse reaction reports to medicines licensed across the EU. Such reports are received from the EU regulatory agencies and from pharmaceutical companies. EMEA staffs are dedicated to the upkeep of the database. Information is received from regulatory authorities in the EU and from the companies responsible for particular medicines. This information is then processed and maintained by the EMEA. It is made available for continuous safety surveillance.

Safety Reassurance

The idea that pharmacovigilance centres are a luxury and affordable only in the developed world, has been replaced by a realization that a reliable system of pharmacovigilance is necessary for public health and for the rational, safe and cost-effective use of medicines in all countries. Where no established regulatory infrastructure exists, a drug monitoring system is an effective and cost-efficient means of detecting and minimizing injury to patients and averting potential disaster. This restores the confidence in doctors to prescribe the drug as well as the patients to consume it.

Marketing & Business Strategy

Pharmacovigilance alerts the company and may help avert the potential minefield of drug withdrawal and subsequent legal suits. There are many examples of pharmacovigilance failures becoming disastrous for companies. However, if the company withdraws a drug with suspected serious adverse reaction voluntarily from the market, it adds to the credibility of the company. In the meanwhile, the company can plan to make up for the revenue loss that might ensue following the withdrawal by focusing on other areas. Safety monitoring during clinical trials or post marketing can at times yield unexpected benefits to the companies in terms of label expansion or at times a totally new indication altogether. Two such interesting examples are the leading lifestyle disorder drugs "Sildenafil Citrate (Viagra)" for erectile dysfunction and "Minoxidil" for hair loss treatment, both were chance discovery and not intentionally developed for those indications, they were actually side-effects of the treatment they were originally developed for. Even if side effects monitoring don't turn out to be a gold mine all the time, they will certainly help pharma companies safeguard their interests.

IT Intervention In Pharmacovigilance

IT can help pharmaceutical companies standardize the procedures for safety management across product lines and geographies. A common and consistent platform will help standardize the site specific processes and reporting across locations. IT can facilitate the pharmacovigilance processes in these following areas:

Safety Surveillance and Detection

Centralized and standardized safety repositories will facilitate in consistent safety reporting. These IT reporting tools can assist companies in determining the reportability of adverse event cases based on the attributes of the case and the reporting requirements of different regulatory authorities. It will also help in instantaneous response to requests for information from competent authorities regarding safety surveillance.

The repository of data gathered from operational data and other sources also known as data marts can help pharmacovigilance personnel identify signals through systematic examination of adverse events using statistical / mathematical tools. This might further facilitate in identification of unusual or unexpected product-event combinations. Data mining can be effectively used to enhance the existing signal detection strategies by assessing patterns and events associated with drug-drug interactions.

Risk Minimization – Performance Linked Access System

Risk Minimization Action Plan (RiskMAP) is a recommended strategic safety program by the US FDA. It is designed to meet specific goals and objectives in minimizing known risks of a product while preserving its benefits. To achieve these goals one or more tools are used. EMEA recommends a similar proactive strategic safety program called Risk Management Plan (RMP).

Decisions to develop, submit, or implement a RiskMAP are always made on a case-by-case basis, but several considerations are common to most determinations of whether development of a RiskMAP may be desirable based on:

- Nature and rate of known risks versus benefits
- Preventability of adverse effects
- Probability of benefits

Many processes or systems to minimize known safety risks are available or under development for use in Risk minimization. These systems typically include:

- Targeted education and outreach to communicate risks and appropriate safety behaviors to healthcare practitioners and/or patients
- Reminder systems, processes, or forms to foster reduced-risk prescribing and use
- Performance-linked access systems that guide prescribing, dispensing, and use of the product to the target population and conditions of use are most likely to confer benefits and minimize particular risks. Figure-3 is a diagrammatic representation of a Performance Linked Access System.

Adverse effects that can be minimized or avoided by preventive measures around drug prescribing are the preferred candidates for RiskMAPs. (Refer case study on RiskMAP- Performance Linked Access System in the box).

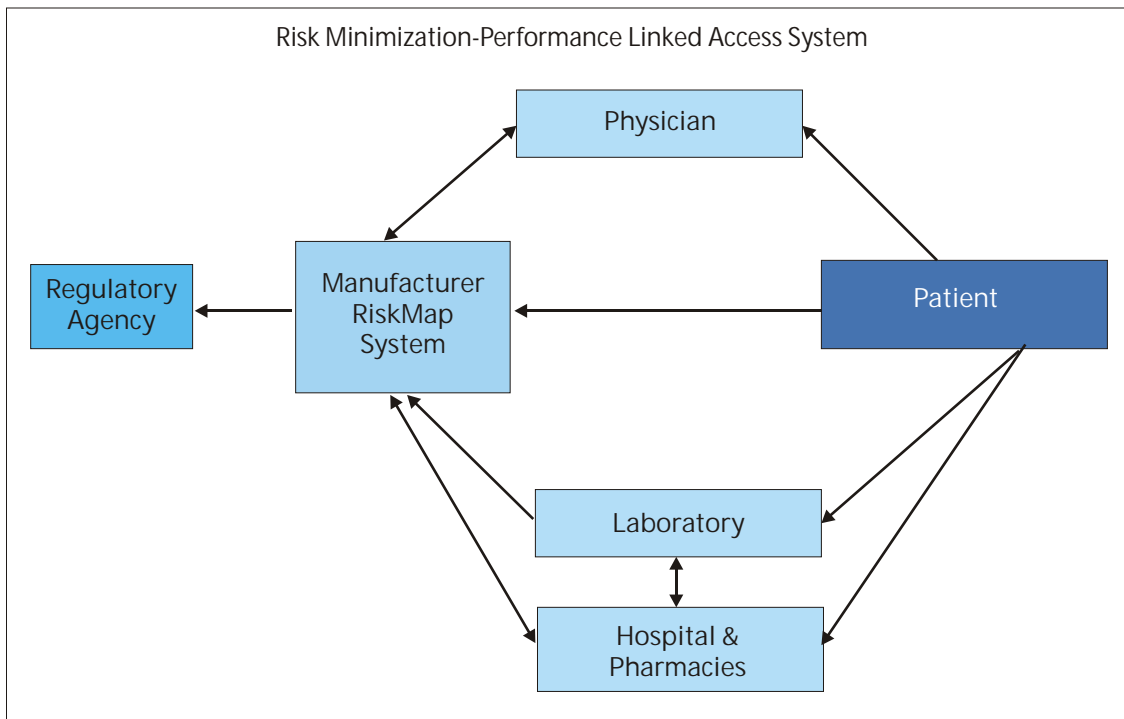


Fig 3: Risk Minimization-Performance Linked Access System

Case Study on RiskMAP – Performance Linked Access System

A world leader in discovery, development, manufacture and marketing of prescription medicines, encountered a business challenge in monitoring the treatment with a highly effective drug that had a known side effect of agranulocytosis. This pharma giant wanted a patient monitoring system which will show up alerts whenever the patients taking the drug start showing signs of developing the adverse side-effect. The application had to be designed to allow for monitoring of the patient by doctors, hospital personnel and pharmacists for timely reduction of the medication, whenever alerts showed up.

Tata Consultancy Services (TCS) developed a Performance Linked Access System (PLAS) for the pharma giant way back in 2003 to monitor the side effects of the drug. The system collects data from different users and centres related to patients, like blood history and other medical test results. This centralized data enables the system to assess the condition of the patient and sends a report to monitoring personnel like doctors or pharmacists. Alerts will be generated to indicate critical conditions. Alerts are auto-faxed to the concerned personnel. Physical location of the patients and medical test schedules can also be tracked using the system. Reports provide an overview on the varied information monitored by the system.

The system was developed on Windows 2000 platform using a three-tier architecture approach with a .NET front end. The system uses COM business components for business logic.

Report Submission

With the emergence of the E2B electronic data interchange standards, companies can design ESTRi gateways (Electronic Standards (for the) Transmission (of) Regulatory Information), systems for importing, exporting, submitting case safety reports, track submission acknowledgements and notifications. These ESTRi gateways can be established to enable not only transmission of electronic Individual Case Safety Reports (ICSRs) to regulatory authorities but also help in sharing of safety data with affiliates and partners around the globe and also meet country-specific local reporting requirements. This will help pharmaceutical companies streamline their business

processes, help protect data integrity, shorten the time required to submit safety data, speed up recipients' response time and help decrease the use of paper-based practice. By implementing such systems companies can also be assured of seamless connectivity and process visibility with the world's major regulatory agencies.

Figure-4 is a diagrammatic representation of pharmacovigilance process with IT intervention for adverse events (AE) management:

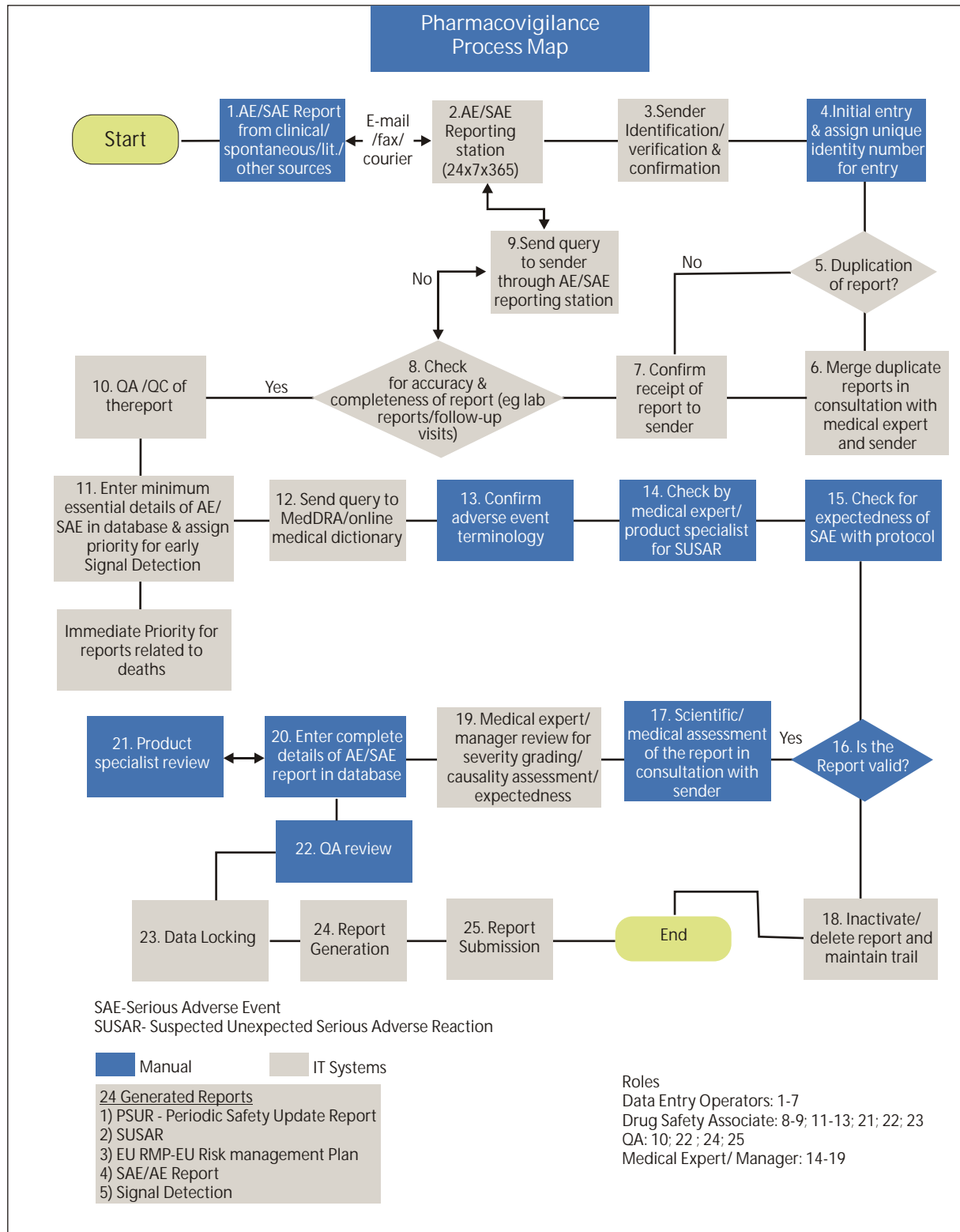


Fig 4: Pharmacovigilance Process Map

TCS proposed Pharmacovigilance Solution

TCS has already aligned itself to this pharmaceutical industry need and its lifesciences and healthcare practice has started a solution-service initiative in the pharmacovigilance area to help pharmaceutical companies in managing their pharmacovigilance activities efficiently.

TCS is providing prepackaged continuous safety and surveillance environment for safety reporting, pharmacovigilance, signal detection and analysis thus providing an integrated and proactive pharmacovigilance program. This solution will facilitate in capturing case related data reported by medical practioners /trial nurse/ pharmacist through a reporting station to the central repository. The assigned safety manager will also collate adverse events reported in public databases and literature in this central repository. The adverse events reported in clinical trials can be transferred into this central AERS database. The adverse events will then be coded using MedDRA. The data in this repository will be used for assessing and managing the adverse events and for expedited reporting, periodic reporting and annual reporting. The solution will support both the export and import of safety cases in E2B format.

An analytical tool will be used on this consolidated data for determining safety signals. The solution will also facilitate the Pharmaceutical Company to closely monitor their Pharmacovigilance program with data substantiated from defined key process indicators reports. This will help in improving operational process bottlenecks.

This program will provide a comprehensive safety management solution along with best in class services for managing the entire safety data of a pharmaceutical company.

Conclusion

In the wake of high profile drug withdrawals from the market due to adverse events, regulatory authorities are enforcing stricter guidelines for new drug approval and post marketing surveillance. Drug withdrawal due to severe adverse effects can cripple organizations and has far-reaching consequences. The company not only loses financially due to litigations but it also loses its credibility in the eyes of its customers and shareholders. Pharmaceutical companies are realizing the importance of having advanced pharmacovigilance systems as they are vital for detecting new safety signals. With innovative IT solutions the safety monitoring of drugs can be enhanced further thereby fostering a sense of trust in doctors and patients in the medicines they use. This will extend confidence in the health service in general and in the long run help pharmaceutical industry achieve the goal of delivering personalized medicine.

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