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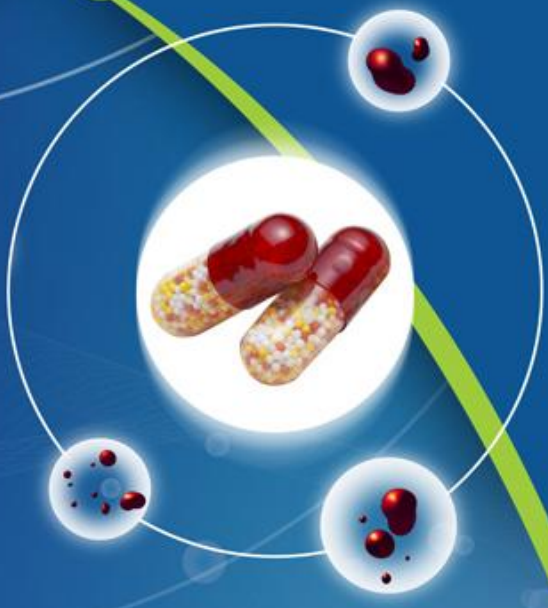

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Review Article

DRUG SAFETY AND PHARMACOVIGILANCE

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ABSTRACT

Pharmacovigilance is related to improve patient care and safety in relation to the use of medicines. It is a public health activity focus on the identification, assessment and prevention of adverse reactions for marketed drugs and also focus on poly pharmacy, iatrogenesis, paradoxical reactions and serious adverse event. Adverse drug reaction may be in the process of pre-marketing or post-marketing surveillance are reported to the regulatory agency and concerned regulatory agency. During 1986 a formal adverse drug reaction (ADR) monitoring system was proposed in India However, nothing much happened until 1997, when India joined the World Health Organization (WHO) Adverse Drug Reaction Monitoring Programme based in Uppsala, Sweden. In India, pharmacovigilance has progressed from the situation as it was in past, an increase in drug safety concerns in recent years with some high profile drug withdrawals have led to raising the bar by various stakeholders more importantly by the regulatory authorities. A very broad definition of a drug "all chemicals other than food that affect living processes." If the affect helps the body, the drug is a medicine. However, if a drug causes a harmful effect on the body, the drug is a poison. The same chemical can be a medicine and a poison depending on conditions of use, dose and the person using it. The word pharmacovigilance has derived from the Greek word pharmacon means 'drug' and the Latin word vigilare means 'to keep awake or alert, to keep watch. Pharmacovigilance as defined by the World Health Organisation (WHO) is 'the science an activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems'. It involves evaluating information provided by health care providers, pharmaceutical companies and patients in order to understand the risks and benefits involved with a particular drug.

Keyword: *Pharmacovigilance, Iatrogenesis*

INTRODUCTION

Drug safety and pharmacovigilance remains a dynamic clinical and scientific discipline. Pharmacovigilance as the processes and science of monitoring the safety of medicines and taking action to reduce risk and increase benefit. Therefore, the assessment of benefit versus risk must begin during the preclinical evaluation of a medicinal product and must extend throughout its full life cycle.

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Pharmacovigilance comprises of:

- Safety data management
- Signal detection for any new altered safety issue
- Signal evaluation and making decisions with regard to safety issues
- Actions, including regulatory, to protect public health
- Informing all concerned parties or stakeholders

Pharmacovigilance is defined by the World Health Organization (WHO) as 'the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem'; it plays a vital role in ensuring that doctors, together with the patient, have enough

information to make a decision when it comes to choosing a drug for treatment. However, despite all their benefits, evidence continues to get those bigger adverse reactions to medicines which are common, yet often preventable, cause of illness, disability and even death. In some countries, adverse drug reactions (ADRs) rank among the top 10 leading causes of mortality. In order to prevent or to reduce harm to patients and thus improve public health, mechanisms for evaluating and monitoring the safety of medicines in clinical use are vital. Pharmacovigilance programs in the next 10 years, describe in brief the potential implications of such trends on the evolution of the science. These days pharmacovigilance is facing lots of challenges to develop better health care systems in this global pitch. Major challenges are globalization, web-based sales and information, broader safety concerns, public health versus pharmaceutical industry economic growth, monitoring of established products, developing and emerging countries, attitudes and perceptions to benefit and harm, outcomes and impact.

A Serious Adverse Event for a molecule could be generated during the preregistration or postmarketing phase. They could occur during clinical trials or be reported spontaneously by a patient, caregiver, relation, doctor, nurse or pharmacist. Another regulatory body or a licencee company could also be the informant. It could be received on phone, mail, fax, journals, newspapers or the latest social media.

Unexpected adverse events could arise anytime in the life of a product. These could put the user to serious risk and could curtail the life of the product. As part of the risk management plan, safety data is gathered throughout the life of a product. Consequently, every company that markets even a handful of products across many countries, gathers thousands of reports per year. The only way to manage this load is using latest software and automation.

As a result, there is now added focus on safety and risk assessment after a product has received regulatory approval, when it is placed on the market and prescribed to large populations. Although there is no international standard that dictates the components of an adequate pharmacovigilance system or the processes to be engaged in risk management, there is consensus among the major regulators that pharmacovigilance is necessary and important in the development and commercialization of medicinal products. Therefore it is essential in building capacity for clinical trials to understand the components, the functions, and the processes required for full and effective pharmacovigilance and risk management.

NEED OF PHARMACOVIGILANCE

The information collected during the pre-marketing phase of a medical drug is inevitably incomplete with regard to possible adverse reactions:

- Tests in animals are insufficiently predictive of human safety
- In clinical trials patients are selected and limited in number, the conditions of use differ from those in clinical practice and the duration of trials is limited
- Information about rare but serious adverse reactions, chronic toxicity, use in special groups (such as children, the elderly or pregnant women) or drug interactions is often incomplete or not available.

AIMS OF PHARMACOVIGILANCE

- Early detection of unknown adverse reactions and interactions.
- Detection of increases in frequency of known adverse reactions.
- Identification of risk factors and possible mechanisms.
- Estimation of quantitative aspects of benefit/risk analysis and dissemination of information needed to improve medicine prescribing and regulation.
- Improve patient care and safety in relation to the use of medicines and all medical and paramedical interventions.
- Improve public health and safety in relation to the use of medicines.
- Contribute to the assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including cost-effective) use.

- Promote understanding, education and clinical training in pharmacovigilance and its effective communication to the public.

ORGANIZATIONAL STRUCTURE OF A PHARMACOVIGILANCE DEPARTMENT

The basic functional "unit" within the pharmacovigilance department is comprised of the drug safety physician (DSP), drug safety associate (DSA), and medical assistant. A "team" may consist of several DSAs, a single physician providing medical review, and one or two medical assistants for administrative support. Depending on the size of the company and the number of employees, pharmacovigilance teams may be organized by product or by therapeutic area, or may be separated into premarketing and postmarketing groups. Matrix structures are common. Global pharmacovigilance departments may exist in a limited number of regional hubs, with each hub having a senior pharmacovigilance member who provides oversight.

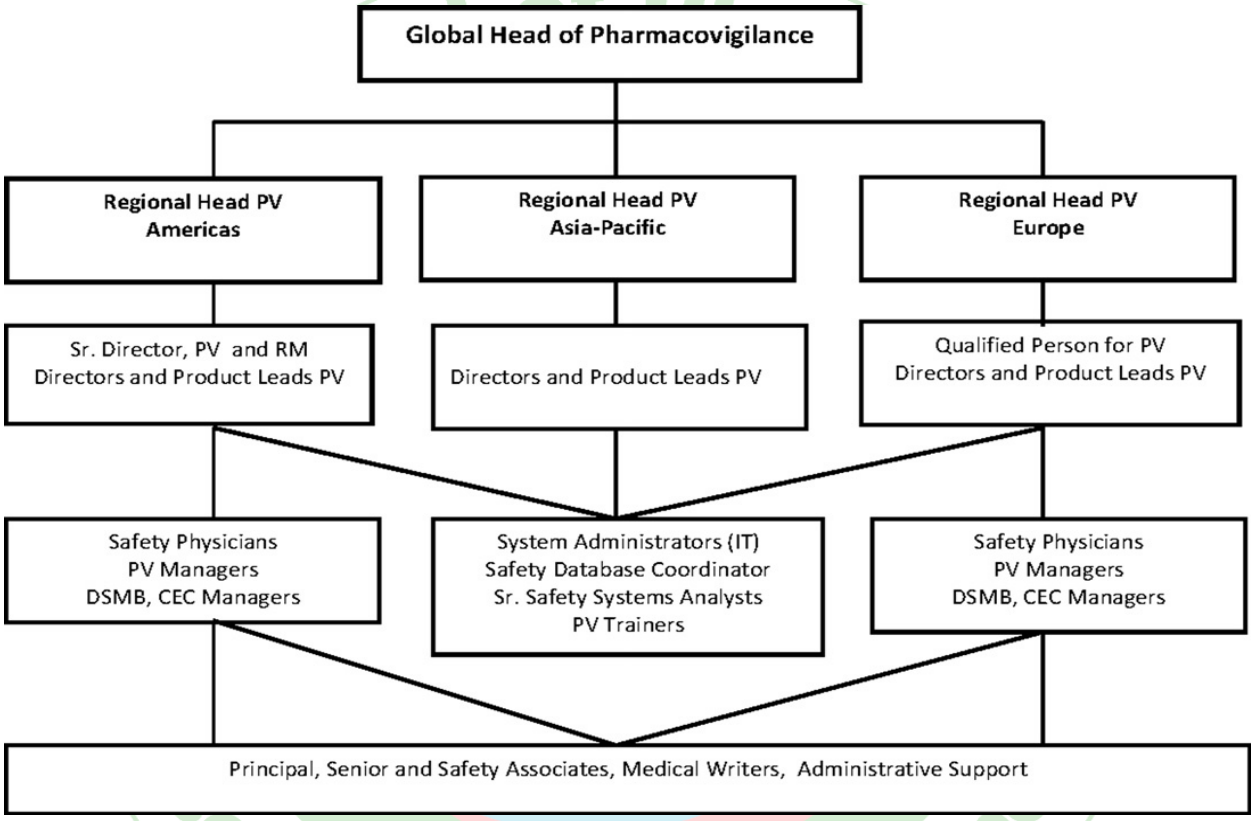

Figure A: Sample organizational structure of a mid-sized pharmacovigilance (PV) department. RM: risk management; DSMB: drug safety monitoring board; CEC: clinical endpoint committee; IT: information technology.

COMPONENTS AND CAPABILITIES OF A COMPLETE PHARMACOVIGILANCE SYSTEM

Based upon the intent and scope of pharmacovigilance, there are certain components and capabilities that are essential to a fully functioning pharmacovigilance system, regardless of how a company's safety department is constructed. These include:

- A qualified person for pharmacovigilance (QPPV) (Europe)
- Safety systems (database) support
- Safety case processing and review
- Medical writing and aggregate reporting
- A sound quality management system including standard operating procedures (SOPs), quality standards, metrics, and training
- Signal detection and risk analysis
- Global safety reporting

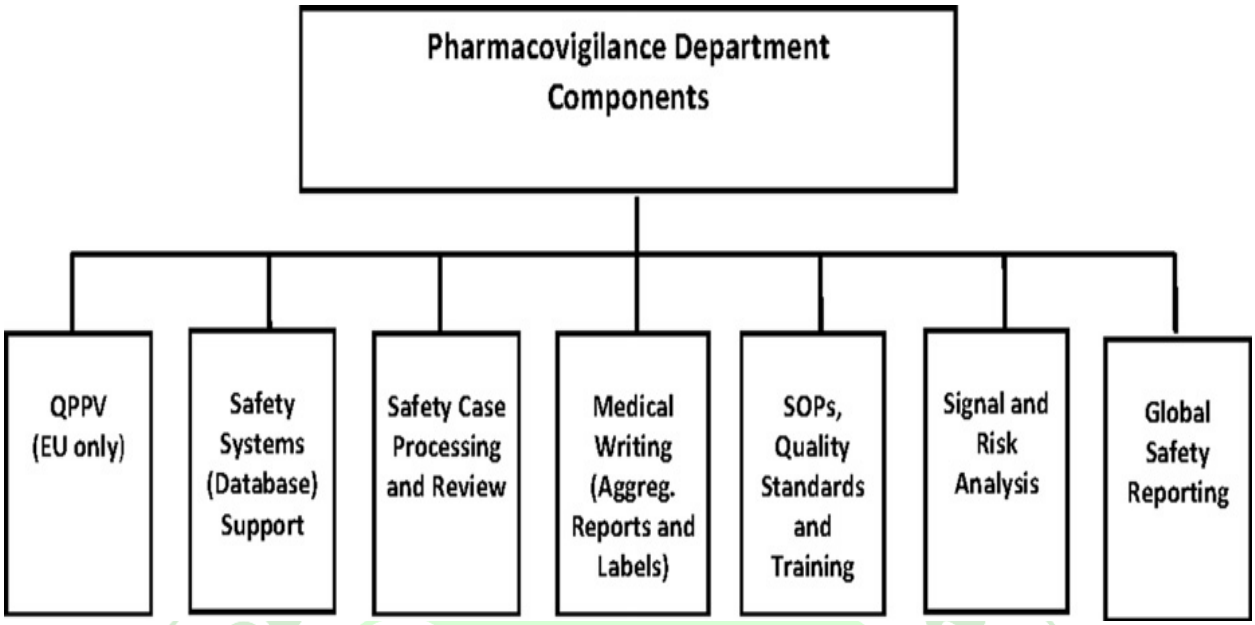

Figure B: Components and capabilities of a fully functional pharmacovigilance system. QPPV: qualified person for pharmacovigilance; EU: European Union; SOP: standard operating procedure.

Basic steps in Pharmacovigilance Case Processing

- Data collection and verification
- Coding of adverse reaction descriptions
- Coding of drugs
- Case causality assessment
- Timely reporting to authorities

Data Collection and verification:

Acknowledgement : A valid case needs to have four elements; an adverse event, a reporter, a patient and a drug. Every report needs to be acknowledged, more so the valid reports. Acknowledgement establishes a contact with the reporter for more information whenever required . It builds company image with the stakeholder and also protects from litigation. A consentious reporter may continue to send the same report repeatedly till it is acknowledged, hence this simple action avoids duplication.

Duplicate search: Due to, greater awareness , stringent regulations and multiple reporting sources, duplicate reports is a common phenomenon. Every safety management software has a facility to identify and delete duplicates. . Certain characteristics of a case (sex, age or date of birth, dates of drug exposure, clinical trial code, country, etc.) may be used to identify duplicate reporting. This action is of significance for further processing of the case. The duplicate could actually be follow up information that could alter the seriousness and hence reporting timeline of the case. Missed out duplicates could send misleading information to signal detection systems.

Triage: Collins dictionary defines triage as

- (Medicine) the principle or practice of sorting casualties in battle or disaster or other patients into categories of priority for treatment
- (Government, Politics & Diplomacy) the principle or practice of allocating limited resources, as of food or foreign aid, on a basis of expediency rather than according to moral principles or the needs of the recipients

Triage in safety means prioritizing the case for reporting to authorities. An oversimplification of triage would be to report deaths and life threatening unexpected reports in 7 days and other adverse reactions in 15 days as there are

also other occasions where expedited reporting is required.

Data Entry: A seemingly repetitive and inconsequential step in the process but something that forms the basis of good reporting. The quality of data entry affects the further processing of the case. Details of the four pillars of a valid case have to be reported meticulously. Patient information has to follow the HIPPA code for confidentiality. Reporter information has to clear and detailed enough to be able to contact the person if necessary. Drug identifiers like name, formulation and dose have to be captured correctly. Event report has to be detailed enough for the evaluator to decide on the cause of the adverse event. This would include chronological description of the event or events, nature, localisation, severity, characteristics of the event, results of investigations and tests, start date, course and outcome, concomitant medications and other risk factors .

Case narrative: Provides summary of events to readers who do not have access to original data sets. During the course of safety data management, it is seen and used by various groups like case reviewers to decide seriousness, upgrade etc , affiliate companies to triage for their countries, , during preparation of PSURs and other summary reports and also by regulatory authorities. One should ensure completeness, chronology and sufficient detail in a narrative so that the reader is able to come to a conclusion.

Coding of adverse reactions: This step ensures that everyone is talking the same language and the data can be shared internationally, Most commonly used system is the MedDRA(Medical Dictionary for Regulatory Activities). Use of MedDRA has lead to a global standardization across regulatory agencies, across companies & across countries. This step usually needs oversight by a medically qualified person.

Coding for drugs: Both the suspect drug and concomitant medication have to be coded. The principle is again to be talking the same language across countries, companies and regulatory bodies. Most common dictionary is the WHO Drug Dictionary enhanced. This is provided as a product by the Upsala Monitoring centre of the WHO. Entries are updated 4 times a year. The majority of entries refer to prescription-only products, but some over-the-counter (OTC) preparations are included. The dictionary also covers biotech and blood products, diagnostic substances and contrast media. For chemical and therapeutic groupings the WHO drug record number system and ATC classifications are considered.

Causality assessment: Non spontaneous case reports usually indicate whether an adverse drug reaction is suspected due to the administered drug. In these circumstances and even otherwise, a causality assessment is required to be conducted. Various approaches have been developed for the structured determination of the likelihood of a causal relationship between drug exposure and adverse events. These systems are largely based on following considerations:

- the chronology or association in time (or place) between drug administration and event
- current knowledge of nature and frequency of adverse reactions due to the suspect molecule; or the pharmacology
- medical or pharmacological plausibility based on signs and symptoms, laboratory tests, pathological findings, mechanism of action
- likelihood or exclusion of other causes for the same adverse events; often the disease condition or concomitant medication.

Timely reporting to authorities: this is the end goal for which all the above has to be done in a timely manner. The reporting could be by sending data back to the sponsor or by a click of a button based on the software used. The latter will provide an extra couple of days for case processing.

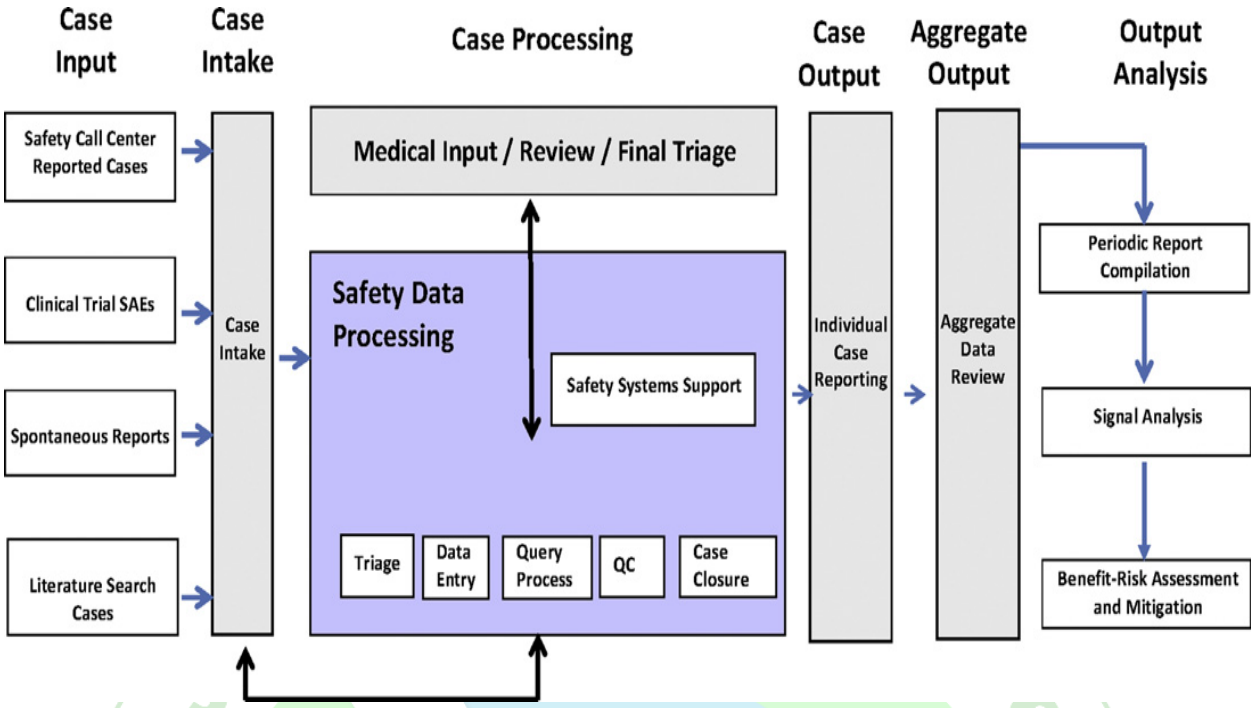

Figure C: Summary of the Basic steps in Pharmacovigilance Case Processing. SAE: serious adverse event; QC: quality control.

Safety data management is the most basic step in pharmacovigilance. This is often outsourced so that internal company resources can focus on the domain related, mentally stimulating activities like signal detection, regulatory responses, information to stakeholders.

STANDARD OPERATING PROCEDURES, STUDY-SPECIFIC PROCEDURES, AND SAFETY PLANS

The number of SOPs related to pharmacovigilance may vary from few in number to many, depending upon the length and complexity of the processes involved. Companies with few SOPs may write individual study-specific procedures (SSPs) consistent with their SOPs, but which provide more detail in relation to a specific product under development. Sometimes all of the pharmacovigilance procedures are combined into a safety plan, or pharmacovigilance plan, which becomes a summary of all of the processes to be followed by the assigned staff in conjunction with the clinical trial or across trials. In Europe, a detailed description of the pharmacovigilance system must be included in the marketing authorization application.

At a minimum, SOPs/SSPs should cover the following activities:

- Serious adverse event reporting.
- Safety case handling (intake, process flow, assessment, documentation, archiving).
- Safety database.
- Safety data conventions.
- Review of patient (clinical/laboratory) data.
- Aggregate data review.
- Signal detection.
- Unblinding.
- Regulatory reporting of safety information and 24 hour safety coverage.

Other SOPs/SSPs are developed as relevant to the specific product or therapeutic area. At the beginning of each trial safety reporting timelines should be reviewed, the timeframes for ongoing review and assessment of patient data should be agreed upon, and the assignment of any unblinded staff should be determined. Studies utilizing a drug safety monitoring board (DSMB) or clinical endpoint committee (CEC) will have additional SOPs/SSPs or charters created to clearly define the roles and processes to be performed by these groups. In addition to written procedures, regular teleconferences and/or

meetings should be held to ensure adequate communication of information, make modifications in best practices as needed during the study, and maintain compliance and audit readiness. Because processes may change during a clinical trial, training is an important part of pharmacovigilance and risk management.

TERMINOLOGY USED IN PHARMACOVIGILANCE

- **An adverse drug reaction (ADR)** is 'a response to medicine which is noxious (an unexpected therapeutic response) and unintended, and which occurs at doses normally used in man'.
  An unexpected adverse reaction is 'an adverse reaction, the nature or severity of which is not consistent with domestic labelling or market authorization, or expected from characteristics of the drug'.
- **A drug or medicine** is 'a pharmaceutical product, used in or on the human body for the prevention, diagnosis or treatment of disease, or for the modification of physiological function'.
- **A side effect** is 'any unintended effect of a pharmaceutical product occurring at doses normally used by a patient which is related to the pharmacological properties of the drug'.
- **An adverse event or experience** is defined as 'any untoward medical occurrence that may present during treatment with a medicine but which does not necessarily have a causal relationship with this treatment'.
- **A signal** refers to 'reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously'.

CONCLUSION

Pharmacovigilance is like a sunshade to describe a processes for monitoring and evaluating ADRs and it is a key component of effective drug regulation system, clinical practice and public health programmes. Pharmacovigilance and risk management are an essential part of pharmaceutical product development and commercialization, the activities of which are highly regulated in many parts of the world. Rare adverse events may not be identified until large numbers of patients receive the product, so pharmacovigilance and risk management must extend throughout the product's life cycle. Benefit and risk must be continually assessed as more is learned about the product through its use. Building pharmacovigilance and risk management capacity requires a systematic approach to ensure that all safety aspects are monitored and addressed properly. Since capacity building takes time and resources, outsourcing of certain activities may enable capacity building to proceed before all capabilities can be done in-house. The use of a limited number of safety centers is a viable and cost-effective option, provided there are good processes, good tools, and good communication of responsibilities and events.

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