Operational Aspects of the Drug Safety Function Within a Pharmaceutical Company

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Introduction

This chapter focuses on the operational aspects of the drug safety function as related to the adverse event reporting process within a pharmaceutical company, placed within the context of basic functions and best practices. The discussion of the process will also include the key contributory roles of technology, quality control and training, as well as recommendations for working with external partners and sharing information with external stakeholders.

Overview of the case-handling process

A drug safety department in a pharmaceutical company performs many functions, although corporate structures in the pharmaceutical industry are extremely diverse in how the drug safety function fits within the company. Drug safety work may be performed within the regulatory function, the medical affairs function, the clinical development function, or as an independent area. The remit of drug safety may also be variously defined to include medical information activities, product complaint management, submission of regulatory documents, pharmacoepidemiology and/or safety support of clinical trials, as well as safety surveillance and other pharmacovigilance activities. However, the task most common to all safety departments is the reporting of adverse events to health authorities according to regulatory requirements. The process of collecting, processing, analysing, and reporting adverse event (AE) information will be collectively referred to here as the case-handling process. In addition to maintaining regulatory compliance, this process is a key component of pharmacovigilance. As discussed in Chapter 8, effective monitoring of drug safety not only requires a systematic approach to collection of information, but a means of organizing that information into a database that allows retrieval in a format amenable to screening and analysis. Much of the safety data available to a pharmaceutical company regarding its products arises from individual reports of AEs. Without effective management of this data...
through the case-handling process, pharmaceutical companies would be less able to understand the evolving benefit-to-risk balance of their products in order to act responsibly in protecting patients (CIOMS, 1998).

Specifics of the case-handling process

Introduction

The case-handling process may be defined as the process by which single case reports of AEs (from clinical studies or from marketed use) are collected, evaluated and communicated. This process forms the basis for an important part of the generation of safety signals and is a necessary prerequisite for enabling the company to comply with international regulations for reporting to regulatory authorities. Although this may vary widely between companies, certain common tasks exist. These tasks may be performed by different skill types, or they may be performed in slightly different sequences, but the steps described in this section provide the basic framework of almost any case-handling process.

The five basic steps in the case-handling process

The basic steps of the case-handling process are shown in Figure 11.1. Each of those individual steps is now discussed.

![Diagram of the case-handling process]

**Figure 11.1** Overview of the case-handling process

*Step 1: Case receipt*

Companies receive AE reports from a variety of sources via a wide range of methods. Each method of case receipt has special case-handling considerations, but the one absolute requirement for all is that the date of receipt by the company or company’s agent must be captured and recorded, since this becomes the clock start date for regulatory reporting (Figure 11.2).
Telephone calls. Consumers and healthcare professionals may call the company to complain specifically about side effects they believe to be caused by medications, or they may call the company for other reasons, for instance to obtain reimbursements or medical information, and incidentally mention an AE. The company employee or agent taking the call must be sufficiently trained not only to recognize AEs, but also to know what information should be collected concerning the event. Additionally, it is essential to obtain contact information enabling further follow-up with the reporter. If the calls are received in an area outside of the safety department, then a means must exist to transmit the information quickly.

Facsimile transmission. Although paper facsimiles, or ‘faxes’, have the advantage of providing automatic confirmation and date stamping, frequently there are legibility problems with the fax copies, and the use of faxes increases the amount of paper that must be tracked and archived. The use of ‘e-fax’ technology, in which faxes are automatically scanned into an electronic document that is received via electronic mail, allowing them to be viewed on-line and stored electronically, mitigates this problem.

Standard mail. Since letters containing AE information may conceivably be received by anyone in the company, it is essential that all personnel are trained in recognition of AEs and understand that this information needs to be forwarded to the safety department as soon as possible. This training needs to include the highest levels of management within a company, since many times such letters are sent to the president or CEO of a company. The legal department is also a frequent recipient of such correspondence, and every effort must be made to ensure that the safety department is notified promptly.

Electronic media. This category includes company electronic mail systems, company Web sites, Internet chat rooms, diskettes and compact discs, and electronic data capture systems used in clinical trials. Although the regulations do not require companies to search the Internet for AE reports, companies are required to monitor any company-sponsored Web sites for potential reports. The issues with electronic media are mainly issues of validity and verification.

Step 2: Case triage

Within the context of the case-handling process, triage is the assessment, classification and prioritization of the information received according to key regulatory, scientific and medical criteria in order to determine what route for processing the case should follow (Figure 11.3). This is the most important step in the case-handling process, when one considers the impact
on the rest of the workflow as well as the consequences of triage errors, e.g. late regulatory reports, missed safety signals and/or waste of case-handling resource. Key issues for consideration in the triage process include the need for clear communication of triage decisions to subsequent participants in the workflow of the case, adequate knowledge level of those involved in triage, and the need for appropriate checks and balances to ensure that errors are caught early. Triage should be performed as early in the process as possible in order to ensure compliance with regulatory reporting timelines. Since this critical step in case handling has such a huge impact on the overall work of drug safety, experienced and qualified safety personnel should always supervise triage.

**Step 3: Case processing**

For the purposes of this chapter, case processing (Figure 11.4) is the creation of a case in the safety database from source information. Case processing includes the tasks of data entry
into the safety database from source documents, coding (AEs, medical history, concomitant conditions, concomitant medications, etc.), writing the case narrative and identifying missing information that should be pursued in follow-up.

**Step 4: Case review**

All cases should be reviewed after processing to ensure that regulatory, scientific and medical standards are met. Case review (Figure 11.5) may be characterized as a two-step process:

- quality review (see Figure 11.6)
- medical/scientific review (see Figure 11.7)

![Figure 11.5 Step 4: Case review](image1)

![Figure 11.6 Step 4.1: Quality check](image2)

![Figure 11.7 Step 4.2: Medical/scientific review](image3)

The key difference between the medical/scientific review and quality review concerns the focus of the review, rather than who does it, when it is done, or how it is done. The appropriate focus of the quality review should be:

- confirmation of the triage assessment of regulatory reportability;
- consistency of data-entry with source documents.
- consistency with established report standards (ICH, 1995).
In contrast, the appropriate focus of the medical/scientific review should be:

- Appropriateness of the AE terms selected.
- Confirmation of the seriousness classification of the AE terms.
- Agreement with the listedness/expectedness classification of AE terms.
- Agreement with outcome classification.
- Agreement with the coding of AEs, concomitant conditions, and medical history.
- Review of the narrative to ensure that it makes clinical sense and includes all important elements (the 2001 CIOMS V Working Group Report contains an excellent description of key components of AE report narratives).
- Authoring the company clinical comment, including determination of the company causality assessment, when appropriate.
- Identification of any specific additional information needed for medical assessment purposes other than routine follow-up requests required for case completion. Pursuit of follow-up on single case reports should be tailored according to the importance of the case in terms of attempts made and methods used (CIOMS, 2001).
- Consideration of ‘upgrade’ or ‘downgrade’ to the case’s regulatory reportability classification.
- Identification of potential safety signals.

A rapid and clearly understood error resolution process must support case review.

**Step 5: Case completion**

The case is considered ready for completion when it has gone through triage, processing, review and approval. The case completion process (Figure 11.8) includes any updates to the case as required by the review cycle, incorporation of additional information requests into standard follow-up requests, generation of a final report and distribution of the final report to appropriate internal and external parties, which may include regulatory submission. Case

![Figure 11.8](image-url)
completion also includes archiving the report and the accompanying source documents. Strategies for document management should allow for paper as well as electronic storage.

**Periodic safety updates**

**Introduction**

In addition to the processing of individual case safety reports, drug safety departments are expected to collate, evaluate and report aggregate analyses of AE cases. Examples of these aggregate reports include the US Food and Drug Administration (FDA) periodic reports, International Conference on Harmonization (ICH) periodic safety update reports (PSUR) and European license renewals. This section will focus on PSURs, in particular on the process for the collection, review and analysis of aggregate safety data.

Re-evaluation of the benefit/risk ratio of a drug is usually not possible for each individual adverse drug reaction (ADR) case, even if serious. Therefore, PSURs present the worldwide safety experience of a medicinal product at defined times post-authorization, in order to:

- report all the relevant new information from appropriate sources;
- relate these data to patient exposure;
- summarize the market authorization status in different countries and any significant variations related to safety;
- create periodically the opportunity for an overall safety re-evaluation;
- indicate whether changes should be made to product information in order to optimize the use of the product (ICH, 1996).

**Overview of the periodic safety update report document**

Pharmaceutical companies are responsible for providing safe and effective drugs. To meet this responsibility, companies are expected to collect safety data on their medicinal products, perform pharmacovigilance throughout the entire life cycle of a product and provide accurate information to healthcare professionals and patients. In addition, companies are expected to keep regulatory authorities informed of the results from the ongoing safety evaluations of their drugs. A standard format for reporting safety evaluations to health authorities is the PSUR.

According to the current ICH E2C guideline (ICH, 2002), see Chapter 9, the PSUR should contain all relevant safety information collected within a specific time period along with a clinical evaluation of the data. Ideally, the data lock point or cutoff date of the PSUR is based on the date of the first market authorization for the drug, i.e. the International Birth Date. In general, authorities require a PSUR for a drug to be submitted every 6 months for the first 2 years after approval, annually for the next 3 years and every 5 years thereafter.

The PSUR consists of the following sections.

1. **Introduction.** A brief description of the purpose of the document, time period covered and reference to previous PSURs.
2. **World-wide marketing authorization status.** Tabular presentation of trade names and marketing authorization dates for all countries.

3. **Update of regulatory authority or marketing authorization holder (MAH) actions taken for safety reasons.** Details of the types of action relating to safety that were taken during the reporting period.

4. **Changes to the reference safety information.** A listing of specific changes made to the reference safety information during the reporting period.

5. **Patient exposure.** An estimate of the number of patients exposed during the reporting period along with the method used for calculation.

6. **Presentation of individual case histories.** Line listings and summary tabulations for cases received during the reporting period plus a brief description of cases considered particularly important.

7. **Studies.** A brief summary of any important safety studies and a review of published safety studies from the literature.

8. **Other information.** Explanation of any efficacy-related information collected during the reporting period. Presentation of any important late-breaking information received after the data lock point.

9. **Overall safety evaluation.** A concise analysis of the data collected during the reporting period followed by an assessment of the significance of the data from the perspective of cumulative experience. This experience includes a review of drug exposure in special populations, e.g. paediatric, elderly, organ impaired, exposure during pregnancy, overdose, drug abuse, drug misuse, drug interactions.

10. **Conclusions.** A comment on whether the data presented are in accord with the reference safety information and a description of recommended or initiated actions.

### Collection and preparation of case-related data

The sections of the PSUR that deal specifically with case-related data are Sections 6 and 9. The main case-related components of the PSUR are the summary tabulation and line listing of medically confirmed serious (listed and unlisted) and non-serious unlisted ADR cases, the cumulative tabulation of medically confirmed serious unlisted ADR cases and the summary tabulation of the non-serious listed ADR cases found in Section 6. Effort should be made to ensure that the data contained in the tabulation and line listing are accurate and inclusive. This effort should focus on the following:

- Inclusion of all cases initially received or with significant follow-up received during the reporting period.
• Accuracy and completeness of the key data elements, particularly those related to the patient, adverse experience and drug exposure.

• Accuracy and consistency of the coding of the verbatim adverse experience terms against a standard medical terminology coding dictionary, e.g. MedDRA.

This initial review of the data can be facilitated by the generation of data quality reports that direct the reviewer’s attention to specific data inconsistencies and omissions.

The PSUR line listing provides the reviewer with key information regarding the patient, adverse experience and drug exposure, along with a brief assessment of the case. The data in the line listing are usually sorted by the medical dictionary body system/system organ class and date of receipt of the case by the company.

Although ICH E2C requirements can be fulfilled by providing the summary tabulation and line listing of medically confirmed serious (listed and unlisted) and non-serious unlisted ADR cases, the cumulative tabulation of medically confirmed serious unlisted ADR cases and the summary tabulation of the non-serious listed ADR cases, companies should prepare listings and tabulations that are acceptable to all regulators. This is particularly important when submitting PSURs to the FDA, who require submission of consumer cases in addition to medically confirmed cases. The FDA also requires the submission of all spontaneous cases regardless of causal relationship to the drug. Companies can meet the reporting requirements of most regulators and still follow a consistent practice across all PSURs by including the additional cases in the ICH line listing or by providing the cases in an addendum or optional case listing.

The ICH line listing format is a useful standard; however, the output can quickly become overwhelming in PSURs containing a large number of cases. Therefore, it is helpful in the review process to complement the standard line listing with supplemental data reports. The reports should be in line listing and/or tabulation format for ease of review. Reports containing full case data and narratives could also be provided to allow a detailed review of selected cases. Topics of interest for supplementary review reports include serious medically confirmed unlisted cases received during the reporting period, cases with an outcome of death, cases involving drug use in special patient populations (pregnant women, elderly, paediatric, organ-impaired patients) and safety issues identified during the current review process or carried forward from previous PSURs. If appropriate, the results of the review of the topics of interest should be presented in the ‘Overall safety evaluation’ section.

The topics described above are common to most PSURs and can be delivered to PSUR authors as uneditable or not easily edited output. They can also be delivered in formats that allow sorting and subsetting of the data. However, the computer programs that generate the output are not usually accessible to individuals involved in writing PSURs and analysing safety data.

The complexity and inaccessibility of the underlying computer programs prevent data end-users from generating ad hoc data queries and reports that may be pertinent to the data in the specific PSUR. However, as computer software applications become more sophisticated and user friendly, data end-users will more accurately be able to query, subset and analyse data without the need for technical programming skills. These sophisticated software tools will provide greater data query and reporting flexibility and allow less reliance on preprogrammed data searches and rigid output.
Collection of other safety data

Certain sections of the PSUR, namely Sections 2–5 and 7, contain information relating to drug approvals and regulatory actions (Sections 2 and 3), reference safety information (Section 4), drug exposure (Section 5), studies and published literature (Section 7). In many pharmaceutical companies, the source data required to complete these sections are not readily available to individuals in drug safety departments. In these situations, it is necessary to include a ‘call for information’ step in the PSUR generation process. The call for information ensures that the appropriate business units are informed of the need for the information, the format required and the deadline for delivery.

The information relating to market authorizations, regulatory actions and changes to safety reference information (Sections 2–4) can generally be requested from the regulatory affairs business unit.

Patient exposure data, reported in Section 5, should be solicited from the business unit with access to worldwide sales information, such as global product information, global sales or global marketing organizations. It is important to collect this information from a consistent and reliable source. This will allow year-on-year comparisons of exposure data. Exposure data can be collected as kilograms or units sold for a specific time period and converted to patient exposure using an appropriate algorithm based on the use of the drug. The conversion method should be included in the section.

The clinical studies information contained in Section 7 should be collected from worldwide clinical project or clinical development teams. The purpose of the section is to highlight completed, ongoing or planned studies that provide important safety information that may affect product information. A detailed description and analysis may be appropriate for some studies; however, a simple listing of the study name, brief description of the study, start date, completion date, number of subjects exposed and brief description of the pertinent safety data is sufficient for most situations.

The compilation of published studies should be performed by individuals or groups experienced in search strategies within literature databases, such as library services or information management groups. Only those published studies containing safety information relating to the drug should be included.

Although the current practice within most pharmaceutical companies is to solicit non-case-related data from individual business units outside of drug safety, there is a trend in the industry to integrate data from various databases into a single ‘data warehouse’. Once this is accomplished, the collection and review of these data, particularly the regulatory, clinical and exposure data, can be accomplished within the drug safety units, resulting in a more timely and efficient delivery of information.

Presentation of case histories

Section 6 of the PSUR provides an opportunity for the company to discuss cases of interest, including cases considered particularly serious, unanticipated or related to a particular safety issue. The sources of these types of cases can often be found in the pool of unlisted cases.

Individual cases selected for presentation should be described in narrative format. Groups of related cases should be summarized collectively. Use of the verbatim case narrative should be avoided. Case narratives, particularly those for expedited cases, are usually more
detailed than is necessary for a PSUR. Case narratives may also contain information specific to follow-up expedited submissions that do not fit well in the PSUR context.

**Overall safety evaluation**

The overall safety evaluation for the PSUR is presented in Section 9. This section summarizes the results of the review of the line listings and tabulations, results of the continued analysis of ongoing safety issues and any appropriate safety signals generated through the ongoing pharmacovigilance process.

The organization of the overall safety evaluation section should be based on the types of issues discussed. PSURs with large numbers of cases, lengthy discussion or multiple issues should be based on a body system or system organ class organization, as appropriate.

The overall safety evaluation is followed by the assessment of the cumulative experience of the drug, such as effects of long-term use, effects of use during pregnancy, drug interactions, etc. The source of data for these evaluations is the supplemental data reports described above.

**Managing the periodic safety update report process – scheduling and timelines for delivery**

At any point in time, major pharmaceutical companies will have many drugs on the market with varying market approval periods in different regions of the world. For instance, a drug may have been in the marketplace for over 3 years within a European Union (EU) country and only recently approved in Japan. Under current regulations, the PSUR will be submitted annually in the EU countries but semi-annually in Japan. Additionally, ICH E2C (ICH, 2002) currently requires that PSURs be submitted to regulators within 60 days of the data lock point. Because of these complexities it is essential that companies devise a suitable project management and workload balance approach to the generation and delivery of PSURs. The project management approach begins with a centralized scheduling procedure for PSUR generation.

The source of information regarding worldwide market authorizations is generally the regulatory affairs business unit. Regulatory affairs would be responsible for compiling the PSUR needs for the drug, including reporting period(s), planned and actual submission dates and contact information. Drug safety units could then augment the centralized schedule with milestone dates pertinent to the generation of the PSUR, such as due dates for submission of non-case-related data, document review, approval and delivery dates.

Because the time interval between the data lock point and regulatory submission is relatively short (60 days), particularly for large reports, companies should enforce a strict set of deliverable action points for the compilation, review and delivery of the PSUR. The action points should actually start well before the data lock point to allow contributors to produce accurate and timely information. A sample timeline based on a 60-day submission and ongoing pharmacovigilance is shown below.

Day −28: initiate process

- send out call for information for non-case-related data
meet with contributors to discuss relevant issues, known safety signals and deliverables

Day 0: data lock point
• run draft tabulations and line listings
• perform necessary data clean-up

Day 12: completion of Sections 1–5, 7 and 8

Day 21: completion of first draft of the PSUR
• send draft out for review

Day 35: close of draft review
• revise document and send out subsequent drafts if necessary

Day 45: approval, sign-off and internal delivery of final document
• send to business unit responsible for regulatory submission
• publish document using internal publishing standards
• archive document

Day 60: due to worldwide regulators.

Staffing models for the case-handling process

Definitions and standards associated with the case-handling process are covered in Chapters 1 and 9 and will not be reiterated here. The focus of this section will be on a description of common approaches to case management from both the medical/scientific and the staffing/organizational perspectives.

There are several common staffing models used to organize a case-handling group to deal with AE reports efficiently. There are advantages and disadvantages to all. Below are some brief descriptions.

• Division according to reporting source. Traditionally, this sort of division refers to having one group process reports from clinical trials and another group process spontaneous reports from the post-marketing environment, i.e. post-approval, since safety regulations are similarly divided. However, there may be further subdivision by report source, e.g. one group may handle consumer reports exclusively while another group may handle reports from healthcare professionals, one group may handle reports just from Phase IV trials and another may be focused on earlier phase studies, etc. The efficiencies gained from this type of approach include: decreased training time, since the scope of work is narrowly focused; the ability for the groups to develop a deeper knowledge in their particular specialty; and the potential for developing a closer working relationship with their counterparts in key interface areas, such as clinical teams, because of the increased frequency of interaction. The disadvantage is that there is less flexibility in the ability of staff to cross-cover during absences and peak workload periods. Also, job satisfaction and retention may be adversely impacted if the employees...
feel that the limited variety in their work experience is boring and/or makes them less marketable.

- **Product life-cycle approach.** This structure typically divides products among persons or teams who are responsible for them through the entire product life cycle, from the earliest phase of clinical development until the product is no longer marketed. This ensures that persons processing the reports have in-depth knowledge of the product’s safety profile, and can provide knowledge continuity to others outside of drug safety working with the product over time. The danger is that these knowledge experts may be lost to attrition or become impediments in the process if they do not share their expertise freely. Frequently, the product life cycle approach also utilizes therapeutic alignment, since it makes sense to group similar classes of products or those used in similar indications. This allows focused hiring of persons with backgrounds in the specialty area, which can shorten their learning curve and bring an additional knowledge resource to the group.

- **Therapeutic alignment.** This may not work well for companies with a diverse portfolio, and most companies will have a number of products that fall outside of their main therapeutic areas. If these ‘orphan’ products are distributed among therapeutically aligned teams, then they may suffer from neglect. If a ‘miscellaneous team’ handles these products, then the team may suffer from a perceived loss of status among the teams more therapeutically focused. Also, therapeutic alignment can limit flexibility in staffing coverage.

- **Pooled case approach.** In this staffing model, the cases are assigned as they are received, i.e. the first case is assigned to Person A, the second case is assigned to Person B, etc. This is based on the principles that:

  1. over time, the workload will tend to even out so that no one person has more work than another, and

  2. each person can be expected to process cases within similar time frames.

In reality, this is seldom true, since cases can vary widely in complexity, clusters in case types received frequently occur, compliance can be jeopardized by work overload, and productivity can vary widely from person to person. Additionally, this approach carries the risk that the least experienced person may process the most complex or medically important case. In order for this model to work, some sorting of cases must be done to align expertise with complexity, priority with availability, and case input with case output. If managed appropriately, this model ensures the greatest staffing flexibility, supports knowledge transfer, and, indirectly, employee satisfaction. That being said, it is difficult for this model to work in very large departments without robust tracking mechanisms, and, if there are a large number of products, training time will be prolonged.

Aside from staffing models at the organizational level, there are also staffing models at the role level that should be considered:
• **Data entry model.** In this model, the largest number of employees involved in case handling are devoted to data entry only, e.g. the rote transfer of information from source documents to proscribed fields in the safety database. These roles are supervised by a small number of persons with scientific, medical, and/or regulatory expertise who assess and analyse the cases, but who perform little of the hands-on case processing. The focus of such a model is primarily on regulatory compliance rather than on safety surveillance. This model is similar to the data management model used in clinical trials, although double data-entry is seldom performed. The advantage of this model is that it can handle a large number of cases very efficiently, and relatively cheaply, since it relies on a less expensive staffing pool. Additionally, it is much easier to recruit and train data-entry staff than more skilled healthcare professionals. The disadvantage is that fewer skilled persons means scrutiny of incoming cases is more cursory and less focused, so signals may be missed.

• **Case owner model.** In this model, healthcare professionals who have been trained in safety regulations perform all aspects of case handling. This ensures that all cases are subject to highly qualified scrutiny. The person who first processes the case becomes the ‘owner’, i.e. accountable for the quality, compliance and completion of the case through all initial and follow-up versions, and is responsible for tracking the case through the process, ensuring that required actions, such as physician review and regulatory submission, are performed as required. The disadvantage of this model is that it requires a greater number of expensive skill types, who are frequently difficult to recruit. Additionally, marketplace competition for these types of individual makes them more difficult to retain, especially as the data-entry component of the work may become tedious to these persons over time. Also, for many types of reports this level of expertise may be overkill, since simple non-serious reports of expected AEs may not merit expert scrutiny.

• **Hybrids.** Cost effectiveness and efficiency can frequently be increased by using a combination of the data entry and case owner strategies according to the types of product and report received. For example, if the bulk of incoming reports are from consumers, then it may make sense to use the data entry approach, and reserve the case owner model for serious cases from clinical trials. The available labour pool at any given time may also influence staffing; for example, during a period when local hospitals are downsizing, it may be relatively easy and cheap to recruit nurses and pharmacists to safety work.

• **Matrix model.** In this model, similar to that used by some innovative clinical teams, a cross-functional team comprised of persons with different skill sets and responsibilities work together in a defined process flow to take the ‘raw material’, e.g. source documents, and produce the ‘end product’, i.e. the completed report. This team includes persons outside of the drug safety department who may be performing functions that are traditionally considered to be drug safety roles. For example, there may be a designated safety specialist on the clinical team (or within the clinical research organization (CRO) working with the clinical team) who is the primary contact with the investigator to collect the necessary information. This person may enter the report into the safety database, and then interface with a counterpart within drug safety to ensure
clarity and resolve outstanding questions. The clinical team physician and the drug safety physician partner in the assessment of the case.

Document management personnel (again either internal or external to drug safety), manage the incoming source documents, case files, and archiving. Data management and/or quality assurance personnel may perform quality checks, which enables ongoing reconciliation between the safety and clinical databases. A safety subgroup within the regulatory department may perform additional review and submission of the report. Other members of the matrix cross-functional team could include safety surveillance scientists, epidemiologists, medical information scientists, and those involved in communicating with independent ethics committees (IECs) and institutional review boards (IRBs). The key to the success of the matrix model is to avoid silo thinking, and evaluate each step of the process in terms of best fit within existing functions rather than in terms of traditional or legacy roles.

- **Out-sourcing.** Increasingly, companies are out-sourcing case-handling work to so-called ‘safety CROs’ – organizations that offer a menu of safety-related services ranging from taking incoming phone reports of AE to regulatory submissions of case reports (Chukwujindu et al., 1999). Owing to the set-up costs of such an approach, out-sourcing is most cost effective as a means of handling peak volumes, such as the large number of spontaneous reports typically received after product launch or to handle the large number of serious AE reports expected from a large mortality/morbidity trial. If a company wishes to maintain a complete safety database on its products, a means of data transfer from the CRO must be found, either by electronic import through E2b files, or by giving the CRO access to the company safety database so that they can enter reports directly. Lessons learned from use of CROs in clinical trials would indicate that success of out-sourcing is dependent on a clear understanding of expectations among both parties, robust supporting processes, and good communication.

**Other points to consider**

In summary, consider the following ‘good process principles’, or ‘GPP’, when evaluating a case-handling process:

- Processes should be mapped into categories of work with defined inputs and defined outputs. This will help eliminate redundancies and duplication of effort, as well as define roles.

- Skill sets in the organization must be correctly aligned with each category of work. Efficient staffing is dependent on accurate assessment of the skills needed to perform the work. If it is difficult to find the right skill sets for a role, then one should consider redefining the role.

- To maximize efficiency in time and effort, it is absolutely essential to maintain a linear workflow and minimize hand-offs. Back-loops, which lead to re-work, duplication of effort, and redundancies, should be eliminated.
Technology and the case-handling process

Introduction

Perhaps the most profound change to the structure and function of safety departments within pharmaceutical companies in recent years has occurred as a result of advances in technology. Leaps in the ability to collect electronically, analyse, and store data have revolutionized the case-handling process. However, the benefits of new technology have also brought new policy and process challenges for safety departments. This section will attempt to provide an overview of both sides of this blade of ‘cutting-edge’ technology.

Selection and implementation of a drug safety case-handling system

Although the terms are often used synonymously or interchangeably, for the purposes of this discussion, ‘system’ will be used to refer both to the application for case processing and to the database for storage of case reports. The choice of systems available for drug safety work continues to expand. A number of vendor packages, or ‘off-the-shelf’ systems, currently exist, allowing companies to purchase wholly functional safety systems ready for immediate use, complete with ancillary functions such as training and technical maintenance services. Alternatively, a host of information technology (IT) consultant firms exist that are experienced in helping pharmaceutical companies develop their own custom safety systems for collecting, reporting, tracking and storing case reports. There are pros and cons to both approaches.

Companies are frequently attracted to vendor packages because the system is immediately available, comes with a user-training program and technical support services, and negates the need to expend internal resources on a development program. However, vendor packages are restrictive in terms of flexibility to meet the company’s specific data capture needs, and the vendor may be slow to make requested changes, even when new regulations would seem to require it. Additionally, the instability and volatility of the technical marketplace may result in a company being contractually tied to a totally different corporate entity from that of its initial system purchase – one that may be less customer-focused.

In contrast, custom applications ensure complete company control over system design and the timetable of subsequent upgrades, as well as integration with other company systems. However, development and maintenance are very resource-intensive, both from an IT and a user perspective. Some companies attempt to tread the middle ground by purchasing a vendor package and then modifying it with customization. Although this approach may address specific data capture needs, depending on the level of customization, it may also result in an inability to incorporate system upgrades from the vendor, leading eventually to an outdated system that is as dependent on internal maintenance as a custom system.

When assessing a vendor package for purchase, or when designing an internal system, the following factors should be considered:
• Critical features or ‘must-haves’

1. \textit{Validation}. Any safety system must be fully validated in order to be compliant with regulations. Validation documentation is a frequent focus of health authority inspections, and auditors expect to have access to these documents even when the company was not the developing entity.

2. \textit{System security}. A safety system must have, at a minimum, certain features to ensure the integrity of the data. It must:
   • be compliant with regulations regarding electronic records and signatures;
   • have controlled access
   • have a robust, easily accessible audit trail to track changes to the data.

3. \textit{Technical compatibility}. The safety system must also be technically compatible with company technical platforms and other system interfaces. For example, duplicate data entry could be avoided if personnel in the company call centre could transmit information regarding reported AEs from their database to the safety system through a direct link. Any system that interfaces with the safety system must also be fully validated or the validated state of the safety system is, by definition, compromised.

4. \textit{Storage capability}. A safety system must also have adequate storage capability for long-term use. Adding additional storage at a later date may adversely impact system performance. It is unlikely that one can overestimate the volume of reports that may be received over time. As several companies have found, one well-publicized safety issue with one drug can generate an avalanche of reports for prolonged periods.

• Desirable features or ‘nice-to-haves’:

1. \textit{Easy input and easy output}. Most systems are better at one than the other, but both are essential. The importance of one over the other may be relative to internal company needs. For example, if the safety department has limited resource for data entry, then the ease of input may be valued most. On the other hand, if the safety department has to respond to a lot of queries to support other functions and has limited technical support to do this, then ease of output may be more important.

2. \textit{User friendly}. If data entry and data extraction are intuitive, then the learning curve of new users will be minimized, decreasing the need for long training periods and minimizing the potential for error. Systems developed solely by technical staff, without naïve user input, are notorious for being difficult to learn by persons without an IT background. This tends to be more prevalent among off-the-shelf systems rather than those developed in-house.
3. **Flexibility to support process changes.** The work of a safety department is constantly influenced by many internal and external changes: corporate priorities, product portfolio, organizational structure, regulations, staffing, customer demands, etc. Systems that cannot adapt to these changes can become a liability. A system that only supports one way of working, due to rigidity of the data entry workflow sequence, or an inability to support global as well as local case distribution, will quickly become obsolete.

4. **Detail of supporting documentation.** When evaluating a system for purchase, the quality of the on-line help, user manuals and other documents will say much about the quality of the system itself, as well as the customer focus of the vendor. Additionally, poor training materials mean hidden costs to the buyer, since additional training will have to be developed and provided by the company. When developing a system, the project plan should include ample time and resource for development of the content of these materials, which should occur in tandem with the technical development. This promotes a user–developer dialogue that ensures results meet expectations.

5. **Labour-saving features.** Automated features, such as auto-narratives, auto-encoders, auto-distribution, edit checks, etc., will not only decrease resource needed for data entry, but will also decrease the potential for error. For example, an automated narrative that pulls information from various database fields into a structured format will not only decrease the amount of time spent authoring the narrative, but will ensure that the information in the narrative (patient demographics, drug names and dosages, medical history, etc.) is consistent with the information that appears in other portions of the report form.

6. **Workflow support.** As the volume of cases and the number of staff increase, the ability to generate performance metrics from the system will greatly assist in identifying areas for process improvement, as well as provide data to justify resources to management. For example, automated date generation and tracking will allow analysis of bottlenecks in the process workflow. Automatic routing will ensure that minimal delay occurs in report hand-offs. The ability to generate various management reports to measure productivity and analyse case-load distribution is also helpful.

- **Other issues for consideration**

1. **Level of technical support required.** Many companies only consider the initial system development costs, without considering the continuing costs of long-term maintenance. A vendor package may be relatively cheap in development costs, but expensive in terms of annual licence fees and service fees for continued IT support. A custom system may be expensive in development costs, but may pay for itself with cheaper internal maintenance. The company must also consider availability of IT resource. A large company with an existing IT staff could support internal maintenance, whereas a new start-up company may have to outsource all IT needs.
2. *Ease and consistency of data retrieval.* As a further point to the need for easy output described above, the nature of safety data requires that query results are consistently reproducible and accurate. This is not as simple as it sounds. If the database structure is complex, or if the system query tool is difficult to use, then different people will come up with different results. Needless to say, this could have disastrous consequences for evaluating a possible safety signal or when responding to a query from a regulator.

3. *Flexibility to support different regulatory requirements as well as regulatory changes, especially in regulatory report generation.* Recent regulatory harmonization initiatives have made it much easier to meet basic international regulatory requirements. In today’s business environment, all safety systems should be able to support these, at a minimum. When regulations change, a period of time is allowed for companies to make the required changes to their systems for compliance. However, depending upon the scope of the change, as well as what else is happening at the vendor or company, the time provided may be inadequate to test, validate and document adequately if the system is inherently inflexible or if system support resources are minimal.

4. *Change control process.* Over time, any system will require modifications, some to resolve errors and some to improve efficiency. Regardless of whether the system is customized or purchased, there must be a clearly defined process for technical changes, with unambiguous accountabilities for each step. Testing, validation, and documentation requirements must be just as rigorous as during system development. This is frequently a focus of internal audits and external inspections by health authorities, since change control is key to data integrity and validity.

**Data migration and database conversion**

Once a new system is in place, there is frequently a need to migrate legacy data from the old system or systems. Over time, with system upgrades, data in the existing database will need to be converted into a new database structure. Additionally, company mergers or licensing agreements may also require data migrations and database conversions. (Although data migrations and database conversions have slightly different meanings and technical differences, for the purposes of this discussion the term data migration will henceforth be used to refer to both.) Without due care, these transactions can result in ‘dirty’ data that is incomplete, inconsistent and incoherent. The following paragraphs describe some best practices than can ensure results that maximize data integrity (Steiner et al., 2001).

Any successful data migration must begin with proper planning. The purpose of the plan is to accomplish the following:

- **Define the project scope.** What is the target data for migration (e.g. how many years of data, which fields, which dates, coded or uncoded, what is the volume, what are the data similarities, what are the data differences, etc.)?

- **Analyse costs and alternatives.** Data migration is costly and resource intensive. For relatively low volumes of data it may be more cost effective to hire temporary
data-entry resources to re-enter the data manually into the new system. It may also be cost effective to migrate only the most recent portion of data, and archive the older data in a read-only database.

- **Review business processes.** The migration team (and, in due course, the system users) must have a clear understanding of how the conventions for entering the old data differ from conventions of data entry in the new system, as well as differences in how the systems handle the data. This will require both functional and technical analyses. For example, if the old system was used to record product quality complaints as well as AEs and this will not be the case in the new system, then it may be problematic to separate the data if the old system had no nomenclature to distinguish them.

It is essential that good validation practices be built into the migration process. Not only is this essential for maintenance of data integrity, but the need to clearly describe assumptions and approaches in validation documents will assist the team in identifying potential gaps and areas of confusion sooner rather than later. Additionally, if problems arise later, comprehensive validation documents can be a key resource in identifying the root cause of the issue, as well as its resolution, especially if members of the original migration team are no longer available.

Success of the effort depends not only upon having adequate resources, but also on having the appropriate and knowledgeable resources available. This is a special challenge during merger situations, when personnel may be leaving the company or are reassigned. It may be necessary for the company to provide special incentives in order to secure the knowledge and expertise necessary for the conversion effort. Even the best legacy system documentation will not cover the historical nuances of business processes. Having access to those familiar with the old system can save much time and resource. In addition to early identification and retention of key personnel, there is also a need for a team approach and continuity throughout the project. Roles and responsibilities should be clear, and communication is key.

Flexibility should be built into the conversion schedule. Time frames should be as realistic as possible, and contingency plans should be in place to account for unforeseen problems that are almost certain to arise at the most critical moment. At least one, and preferably multiple, ‘mock’ migrations should be done prior to the final one. In a mock migration, a copy of a representative subset of data from the old system is migrated into a copy of the new system database. This helps to ensure that errors in the migration program are identified and corrected prior to the final effort, when the data is migrated into the ‘real’, i.e. production, environment.

Once the final migration is completed, it is critical to provide post-migration support to avoid continuing problems. Retaining members of the original migration team for the immediate post-conversion period is critical. If consultants are used, then their contracts should include a provision for at least a 2 to 4 week support period post-rollout. It is also important to document and track any migration issues identified by the users. Although no data migration is perfect and some problems will be expected, this will allow the maintenance team to evaluate and prioritize repairs. It is also essential that read-only access to the retired database be retained for some period of time after migration. There is frequently a need to refer to the legacy data in order to resolve errors in the migration, or to use as a resource in data queries. For example, during the initial post-migration phase, it
may be useful to query both databases to ensure completeness and accuracy of surveillance search results until a reasonable comfort level is established. Finally, a ‘top-down’ (e.g. prioritized) and programmatic, automated approach to clean up of legacy data is recommended. Manual data clean-up of individual cases is not only labour intensive, but it can actually result in more discrepancies, with the danger of increasing inconsistencies with the original cases due to individual interpretations and lack of knowledge of legacy processes.

Quality control and the case-handling process

Introduction

In order for the AE information accumulated in the safety database via the case-handling process to be useful in pharmacovigilance, there must be an assurance of the quality and consistency of the data. As described in Chapter 8, although case-handling errors would have to be severe in order for a true safety signal to be completely missed, such random inaccuracies might lead to a delay in detection by diluting the certainty over the association between the AE and the drug. Conversely, data errors may lead to generation of a false positive, or just increase the level of ‘noise’ that must be filtered out to make an accurate assessment. Ongoing continuous quality control is necessary in the case-handling process in order to prevent these cumulative effects from wasting time and resource. Quality control procedures are not enough; there must be an overall quality control system in place to ensure that processes interface and that no gaps exist. The ultimate success measure of a company’s quality control are audits, both internal and external. This section will define quality as it pertains to the case-handling process, describe the underlying principles of good quality control practices, and then provide some advice for how to prepare for an audit, how to behave during an audit, and how to respond to audit findings.

Defining quality

Before something can be measured, it must be defined. As most of today’s concepts of quality were first defined in the product manufacturing area, it is useful to consider this definition of quality. Good manufacturing practice (GMP) defined product quality as the absence of defects and the fitness for use as determined by the end user. These same GMP principles were later applied to good clinical practice (GCP) and thus to the work of drug safety. One may think of case handling as the manufacturing process, and the output of that process, the AE report, as the product. The report should have an ‘absence of defect’ and be ‘fit for use’ by the end customer, e.g. the receiving regulator and others, both internal (safety surveillance staff, clinical teams, etc.) and external (data safety monitoring boards, ethics committees, etc.) With the needs of these end users in mind, quality of an AE case report can be loosely grouped into four categories, the ‘four Cs’ of quality:

1. **Consistent.** The information in the report should be consistent with the source documents, and the report should be processed in such a way as to be consistent with established departmental standards and applicable regulations.

2. **Correct.** The report should be medically accurate, especially in terms of any coding of terms, and the regulatory classification should be appropriate.
3. Compliant. The case should be processed and reported as required by company standard operating procedures (SOPs) and relevant regulations.

4. Complete. Completeness of the report may be thought of on two levels: enough information to make an accurate medical and regulatory assessment of the reported event(s) and/or enough information to complete the required fields of the relevant regulatory reporting form. In most instances these two should be synonymous.

**Improving documentation**

It is impossible to assess consistency, correctness, compliance and completeness without good documentation. The old adage ‘if it isn’t written down, it didn’t happen’ is especially true in quality control. Documentation provides the evidence that the process is defined and functioning, and may be classified into three categories:

1. Documents that specify how something should be done, such as policies, SOPs, guidelines, working practice instructions, coding manuals, data-entry manuals, etc.

2. Documents that capture information and provide evidence of the work performed, such as source documents, individual case reports, summary reports, classification worksheets, review notes, queries, change requests, etc.

3. Documents that provide information about the results of the work performed, such as productivity reports, error reports, compliance reports, etc.

All three types play important roles in quality control of the case-handling process:

- Type 1 documents provide the standards against which the work is assessed.
- Type 2 documents provide the evidence of how the work conforms to the standards.
- Type 3 documents provide the data needed to identify problems and solutions.

The following good documentation practices should be considered. Type 1 documents should reflect the consensus and best practice experience of all involved. This means that SOPs, guidelines, manuals, and other instruction-type references should be written by those with in-depth knowledge of the processes, and be subject to wide review to identify possible gaps or exceptions and eliminate potential conflicts. Special attention should be paid to language in global documents, since certain terms may have different meanings according to the linguistic background of the reader. Additionally, it is important to ensure consistency between overlapping documents, especially in the use of terms and definitions. Subtle text variances may lead to significant differences in interpretation and implementation. Consideration should also be given to external documents, such as regulatory guidelines and software manuals, and the pool of reviewers should be chosen accordingly. Approval should only occur after a consensus is reached. Dates of implementation should be synchronized and tracked.

The biggest challenge for these types of document is ensuring that they are kept up-to-date with real-life practice. Documents that require more time for revision and approval,
such as corporate policies and global SOPs, should be written at a high-enough level so as to minimize the need for frequent change. The lowest level of detail should be reserved for documents such as local guidelines and working instructions that can be updated quickly and easily to meet the changing needs of everyday work. All documents should be subject to version control and review cycles appropriate to change frequency. It is important for documents to have both a routine review cycle as well as a defined mechanism for making an ad hoc change quickly. Changes to more technical documents, e.g. data-entry manuals and coding manuals, should in most instances be aligned with technical changes or updates. It is also important to have strategies in place to minimize errors when changes are made, such as focused training workshops, job aids and visual reminders.

Measuring quality

Once quality has been defined and documented, the process for measuring it also needs to be defined. It is important that the focus is on key areas that have a true impact on quality, not just ‘counting what’s easy to count’ (see Chapter 8). First, the boundaries of the process being measured should be established. For example, when measuring regulatory compliance, choices must be made when determining scope. Will global compliance be measured or will local compliance be measured as well? Will the focus be on submission compliance of expedited single reports or will it include submission of periodic summary reports? Will only external regulatory compliance be measured, or will internal compliance, e.g. compliance with company standards (SOPs, guidelines, etc.) and compliance with internal distribution timelines also be measured? If internal compliance is measured, to what level will that extend: tracking hand-offs at all levels or at a subset of levels – between individual employees, between company departments, between company divisions, such as global units and local marketing companies, between the company and licensing partners, etc? Will this be measured bidirectionally, or just unidirectionally? For example, is it important only to know the compliance of local units sending data to the global headquarters, or is it also useful to track the time frames in which headquarters sends data to the local units?

In determining both the scope and the strategy for measuring quality, the following points should also be considered:

1. **Available resources.** The scope of quality control must be consistent with the available resource; elaborate plans are useless without the means to carry them out. Resource constraints require more prioritization and focus in methodology (Burr, 1987).

2. **Management support.** Sufficient resources (time, money, people, technology) must be allocated to quality control by management. Support for this can be obtained by providing metrics documenting the need, a detailed plan that maximizes efficiency, and examples from internal or external experiences that demonstrate the costs of poor quality (Farrow, 1987).

3. **Company structure.** Quality control is not a one-size-fits-all type of process; it must be tailored to the specific organization, or otherwise risk being inefficient and inaccurate.

4. **Areas of concern.** Quality control should focus on known problem areas, although
analysis of interfaces that may be contributing factors should also be prioritized. For example, a recurring data entry error may be the result of inadequate training.

5. Technology. Technology should be leveraged as much as possible to improve quality control efficiency, but should be seen as an enhancement to, rather than a replacement for, human analysis.

When considering what data to collect in order to measure quality, whether manually or with the aid of technology, it is important that what is collected is:

1. Valid and verifiable. For example, programmed quality control reports should be validated the same as any technical query, and all findings should be supported by documentation.

2. Clear and consistent. Quality control should focus on objective rather than subjective data, and recognize the difference between style and substance. Persons participating in quality control should not only agree on what priorities to focus on, but should agree on common methods.

3. Meaningful and timely. The quality control process cannot add value if the process is so slow that results are outdated by the time the data are analysed, or if the findings are inconclusive because the right data were not collected.

Quality control does not end with data collection. It is not enough to present the number of late report submissions without providing some insight as to why the reports were submitted late. Not only must the overall findings be analysed, but the components must also be analysed. Some types of component to consider are:

- report type (e.g. post-marketing, investigational, etc.);
- report source (e.g. consumer, sales representative, clinical research organization, licensing partner, etc.);
- report origin (country, department, clinical trial, etc.).

Additionally, common contributing factors and trends should be identified:

- training issues
- communication issues
- process issues (especially identification of ‘bottlenecks’ in the process)
- technical issues.

Once the underlying problem is identified, quality control should assist in determining the appropriate corrective actions to be taken. Individual human error may be addressed with retraining and management counselling. Systematic process errors may be addressed with revisions and clarifications to guidelines and manuals. Agreements with outside managers
may be needed to address issues with external contributors to the process (i.e. incomplete reports from clinical study monitors, late reports from sales representatives, etc). Although quality control personnel may not be involved in implementation of the corrective actions, they should be responsible for ensuring that the agreed actions are clearly documented, and should follow up at intervals to ensure that the corrective actions have occurred.

Preparing for internal audits and regulatory inspections

While the discussion below is based primarily on experience with FDA inspections, the basic principles are equally applicable to inspections by other health authorities. The term ‘audit’ will be used to refer to internal company audits, and ‘inspection’ will be used to refer to audit by a regulator. However, all audits and inspections are intended to answer the same essential questions:

- What is the system?
- Is it functioning as planned?
- If not, what is the significance of the findings?

There are three lines of evidence to be pursued in any audit or inspection:

- physical evidence
- documentation
- verbal accounts.

This is done primarily through three corresponding activities:

- physical inspection
- document review
- personnel interviews.

Internal audits are conducted so that company management knows whether company procedures are being followed, company objectives are being met, and whether regulations are being complied with by the department(s) under scrutiny. The goal of this is to prevent damage to the company, to identify areas for improvement, and to provide quality assurance, which can be defined simply as ‘the activity of providing the evidence needed to establish confidence, among all concerned, that the quality function is being effectively performed’ (Gryna, 1988).

Inspections by auditors from health authorities focus almost entirely on regulatory compliance. These inspections may be unannounced and do not occur on a regular basis. The inspection may be ‘routine’, e.g. conducted as part of the normal periodic inspection schedule to verify the accuracy and completeness of the reports submitted to the health authority, or ‘for cause’, e.g. prompted by evidence of non-compliance or suspicion of non-compliance with regulations (CPMP, 2001). The most common reason for a ‘for cause’ inspection of a safety department is late submission of expedited reports.
The best way to prepare for a regulatory inspection is to maintain a state of constant readiness. The preparations described below should not be deferred until notice of inspection is given (should one be so fortunate as to have advance notice) but should be activities that are part of the routine function of the department.

**Document preparation**

Special attention should be paid to ensuring all documents that are subject to inspection are accurate, complete and up-to-date, especially organizational charts, training records, job descriptions, employee CVs, SOPs, guidelines, policies, validation documentation, manuals, and any other procedural documents. All documents should show evidence of change control, including implementation dates, approval signatures, and version control. Employee resumés should include their current position and responsibilities. Regulatory inspectors may not only hold a company accountable for compliance with regulations, but they may also hold the company accountable for compliance with their own internal procedures.

Validation documentation for any application or database used by the safety department should show evidence of compliance with regulations for electronic records. This includes provision for audit trails of all changes made to electronic data and security measures to control access to the system.

Additionally, if the company was inspected in the past, then special attention should be paid to previously identified problem areas. If the company committed to corrective actions, then evidence of the implementation of these actions as well as evidence of their success in rectifying the problem should be collected.

**Employee preparation**

Employees should be educated about the corporate procedures for regulatory inspections. They should be aware of who should be notified, who is responsible for coordinating activities, and roles and responsibilities during the inspection. Experienced persons within the drug safety department should be identified to interact with the inspector. It is also essential that all employees are knowledgeable about the procedural documents applicable to their work, since the inspector may question them as to how they perform their daily work and compare their descriptions to what is stated in the documents. Additionally, the employees should be instructed on appropriate behaviour with an inspector. They should be instructed only to answer the questions asked, and not to volunteer additional information, as well as to admit openly when they do not know the answer to the question rather than trying to pretend otherwise. They should avoid defensive or antagonistic responses or body language, and should maintain a professional demeanour at all times.

**During the inspection**

A representative from the department responsible for managing activities during a regulatory inspection (in most companies, the quality assurance department) should accompany the inspector at all times. A room should be set aside to serve as the place where the inspector will interact with staff, review documents and request information. The inspector may ask to tour the department under inspection or other related areas, but is not allowed to
interfere with the daily work of the company or to conduct the inspection outside of normal business hours.

Frequently, the inspector first asks for a presentation of the organizational structure of the company and the department. This is typically followed by requests for relevant SOPs, which are then reviewed for appropriateness and adequacy. The inspector often focuses on a subset of products in the beginning, although this list may expand. The selection of products is most commonly focused on drugs most likely to have serious unexpected ADRs, drugs that could cause serious medical problems if there is a failure of expected action, drugs approved within the last 3 years, new molecular entities, or those with known or suspected bioavailability or bioequivalence problems. The inspector may arrive with copies of submitted reports that he investigates further. He may also ask for line listings and randomly or selectively choose reports from the list for further analysis. He may ask for individual case reports, source documents, file notes, proof of regulatory submission, follow-up correspondence, customer complaint files, equipment service reports and periodic summary reports. Only documents specifically requested should be provided, and all documents should be reviewed and organized before giving them to the inspector. The inspector is only allowed to keep copies of documents, and these should be clearly marked ‘copy’ and ‘confidential’. Additionally, a list of all documents provided should be maintained.

During the inspection, a plan should be in place to ensure availability of staff for support. Inspectors not only judge a company on its ability to provide the information requested, but also judge them on the speed of response, since this is a key indicator of organizational competence. Technical support should be on hand to run queries, and representatives from other departments that interface with drug safety, such as regulatory and product quality, should be available to provide information or answer questions. If it is apparent that the inspector is focusing on particular products or processes, then the most knowledgeable persons about these areas of interest should be on hand to provide expertise as needed. Additionally, arrangements may need to be made to ensure availability of staff at other company locations, which may be problematic due to time zone differences.

During the inspection, communication strategy is key in avoiding chaos and confusion. Typically, there is a designated ‘inspection room’ where the inspector(s) performs review, questions personnel and requests information. All requests from the inspector should be written and confirmed with him at the time of the request. One or more persons should be available at all times to receive requests from those interacting with the inspector in the designated inspection room. There should be a single point of contact at each location and in each department involved, and all requests should go through that designated person. To avoid delay, designated phone lines and fax lines should be dedicated and monitored at all times. When the request is relayed to others, all verbal communication should be followed with a copy of the written request to avoid misinterpretation.

After the inspection is complete, the inspector typically presents his findings verbally to the company inspection team and relevant management, and indicates what recommendations for regulatory action (if any) he will make. This is an opportunity to discuss the observations and seek clarification from the inspector, but should not be used as a forum for debate. The most common regulatory citations of safety departments include:

- failure to submit expedited reports for serious, unexpected ADRs;
- expedited reports not submitted on time;
• expedited reports that are inaccurate and/or not complete;  
• repeated or deliberate failure to submit periodic summary reports;  
• failure to conduct prompt and adequate follow-up investigation of case reports;  
• failure to maintain adequate AE records for products;  
• failure to have adequate written procedures.

The inspector will issue a formal written report, and the company should respond to the report in writing (usually within a specified time frame). The company response should address each item, clarifying any perceived discrepancies and specifying what corrective action the company will take, as well as what steps the company will take to avoid recurrence of the problem in the future. The health authority may accept the company’s response or may require additional actions by the company if it feels the voluntary plan is inadequate. Once the action plan is agreed the company will be held accountable for implementation, and this is likely to be audited during the next inspection.

Finally, an internal summary of the inspection should be written and circulated to management. The account should be factual and avoid negative language, presenting a balanced description of what went well during the inspection and what did not. Recommendations for improvement in the preparation for, or conduct during, the inspection should be highlighted.

In the event of non-compliance, regulatory actions that may follow an inspection include (CPMP, 2001):

• required education and facilitation;  
• additional inspections;  
• formal warning;  
• public disclosure (publication of names of companies/MAH found to be seriously or persistently non-compliant);  
• formal caution (if criminal offense is admitted);  
• criminal prosecution;  
• suspension of marketing authorization.

**Training and the case-handling process**

**Introduction**

The cornerstone of any successful case-handling process is the training program that supports it. Drug safety departments are held accountable by regulators to ensure that persons involved in safety work are adequately qualified and trained to perform the work required. Training records are a primary focus of both internal audits and regulatory inspections. This section will discuss some best practice approaches to training as it relates to AE reporting (both inside and outside of the drug safety department), as well as provide a high-level overview of some of the new training tools available.
The importance of training records

Training records must be maintained for all personnel in a drug safety department, and are subject to audit and regulatory inspection. In order to ensure that new personnel complete all training requirements, it is helpful to develop a time-based curriculum plan for each role – a detailed, content-focused training schedule with clearly defined objectives and milestones with an accompanying checklist. Along with the traditional employee induction or orientation program, this will not only provide structure to the new-hire training program and prevent gaps in completion of requirements, but will also provide a timeline that helps the employee understand training expectations and provide an objective measurement of the employee’s progress. The curriculum plan ensures that requirements are tailored to what is appropriate for each job description. The checklist can be designed with spaces for dates and signatures so that it provides verification and documentation when each task is completed.

It is also important to establish standards for maintenance of training for existing employees. Personal development plans agreed between employee and manager can be used to customize training to address individual skill gaps, as well as to accommodate pursuit of personal career interests. Annual ‘refresher courses’ for required SOPs and guidelines, as well as retraining when document revisions are issued, should be standard procedure. There should also be an established process for determining the appropriate level of training required when new SOPs and guidelines are issued, e.g. whether attendance at a live course presentation is required, or whether it is sufficient to read the document and sign a statement verifying comprehension. This, too, should be role specific. For example, attendance at a presentation on a new SOP for developing study protocols may not be necessary for a role focused on data entry of case reports, but it would be relevant for a drug safety physician who may assist with authoring a protocol.

Maintenance of training records has traditionally been paper based, but new electronic training tools are easing the burden of keeping these records current. Some of the functions now available include management reports to identify employee training gaps, electronic reminders when retraining is due, on-line calendars of available courses, electronic scheduling and course enrollment, and attendance tracking. Systems that are compliant with electronic records/electronic signature regulations can even serve as the sole repository of training documentation.

Suggested approaches for different audiences

When planning a training program, it is useful to understand the underlying principles of adult learning. Information presented via lectures, reading materials, or audiovisual presentations has been shown to have a retention rate of only 20 per cent or less (Brookfield, 1986). When trainees see a skill demonstrated the retention rate increases to 30 per cent, but if they actually practice a skill, then it jumps to 75 per cent. The highest retention rate, 90 per cent, is obtained when the trainees must teach someone else or immediately use what is learned. Adults learn best when they are allowed to be autonomous and self-directed, and when there are opportunities for practice and feedback (Lieb, 1998). Current research indicates that the most effective training is ‘blended’, e.g. provides a mixture of instructor-led and technology-based methodologies (Herron, 2002).
Internal drug safety staff

Drug safety personnel involved in case handling first and foremost need a basic understanding of the applicable regulations, since this has a direct impact on their daily work. The tight time frames of regulatory reporting are the primary drivers for process flow and task prioritization. Additionally, personnel need to have an understanding of the company interpretation of these regulations, as described in SOPs and other documents. Therefore, it is more efficient to link the two together, not only in the classroom environment but also in reading materials. Comprehension of this material can be enhanced with practical examples. A self-paced learning approach will help each student to absorb these at a rate comfortable for them. Students should be exposed gradually over time to increasing levels of complexity. For example, persons learning data entry should start with simple cases that are not under tight time frames for completion, such as reports of non-serious expected AEs, and gradually advance to more complex cases.

In addition to content, case-handling staff need technical training on the system used to process reports. Robust on-line help, detailed data-entry manuals, and other reference materials are essential. Live data-entry demonstrations and hands-on practice with sample cases in a training database environment are key to preventing new user errors in the validated production environment of the ‘real’ database.

Other members of drug development

Drug safety departments are frequently responsible for providing training to personnel in other areas of drug development, such as clinical study management, clinical research and experimental medicine, who are also involved in collecting and reporting AEs. The best approach for these audiences is to tailor the training materials to focus on the content that is most applicable to their daily work. For example, a clinical trial monitor has no need to learn the regulations for spontaneous AE reporting but does need in-depth knowledge of the requirements surrounding clinical studies. Cutting out the extraneous materials will allow additional time to discuss specifics pertinent to the work of the audience, e.g. requirements for informing investigators, IRBs and ethics committees. Since AE reporting for these roles may be an occasional task, rather than a daily activity, distributing simple step-by-step job aids is helpful in reinforcing the initial training. Whenever possible, the use of standard report templates to collect information will serve as reminders of what information is needed. Identifying an expert resource to be available to answer questions, and making a ‘frequently asked questions’ reference available will also be helpful.

Other company employees outside of the drug development area

All employees of pharmaceutical companies are required to report any AE associated with company products that they become aware of during performance of their work. The most likely other departments where this may occur are in sales, medical information and legal. All need to have sufficient knowledge to identify an AE, understand their responsibility to report these to the drug safety department, and know how to do so and in what time frame. It is important that clear and simple processes are put in place to enable this. However, especially with the sales force, the biggest challenge is to motivate these employees to report, since AE reporting is frequently seen as something that will have negative impact on
their ability to sell the product. Training, therefore, needs to focus on the positive business value of AE reporting:

- **‘Forewarned is forearmed’**. It is always best for the company to know about problems with its products before they become known by the press, competitors and regulators, and the sales force can serve as an ‘early warning system’.

- **Increase credibility with customers**. Prescribers will be impressed with a company concerned with protection of patients, and their comfort level with use of the product will be increased when they see evidence of good pharmacovigilance practices. Providing feedback to them on the results of the company investigation and analysis of the reported AE will also give the sales representative another opportunity for interaction.

- **Improve accuracy of product labelling**. Accurate labelling protects the company and the patients. Additionally, as patient exposure increases, collecting information on AEs may actually provide data that will have a positive impact on the label. For example, percentages of expected AEs predicted by clinical trials may be found to be inaccurately high, evidence may be gained that leads to removal of warnings and precautions, and important information regarding the effects of the product in overdose situations and pregnancy exposures will be gained. There is also the potential that beneficial drug effects may be identified, e.g. minoxidil and hair growth.

Providing real-life examples of the consequences of failure to report AEs can enhance the effectiveness of training. It is fairly easy to find recent instances in the press where a company suffered a significant financial loss because of safety issues. Audiences should also be made aware of potential penalties that may be imposed on individuals as well as companies, such as fines, debarment, and imprisonment. For example, debarment may legally prohibit an individual from future employment by any pharmaceutical company or any organization associated with a pharmaceutical company, which would seriously impair the individual’s ability to earn a livelihood.

**Strategies for maximizing efficiency of the training process**

One of the most commonly used methods for minimizing the resources required for training is the ‘train the trainer’ approach. When resources do not allow direct training of the target audience (e.g. a geographically disseminated group, such as the sales force), the training team can focus on training a subset of representatives who will then return to their respective locations and provide the training to their local groups. For this approach to be successful it is important that the training given to the ‘trainers’ is very focused and intensive, and that training materials provide a greater depth of detail than normal, since the new trainers must be comfortable with the content and be able to answer questions accurately. The drawback to this approach is that the new trainers will not have the background and experience of a true knowledge expert, which may lead to errors in interpretation and decreased knowledge retention over time.

Another frequently used strategy is mentoring, which is based on establishing trainer-level competence in specific areas among a small number of senior staff who can then share
the burden of providing and, even more importantly, reinforcing training among those that they work with on a daily basis. This also provides an additional knowledge expert who is readily available to answer questions that may arise. For new employees, who have completed a basic training curriculum and are ready to begin work, it is frequently helpful to assign them to a mentor or preceptor on the same team who can provide individualized attention to them over an extended period of time. Among the disadvantages of this approach are decreased productivity of the experienced personnel who are mentoring, decreased or delayed effectiveness of training due to personality conflicts between the mentor and trainee, potential mentor burn-out, and the fact that there must be a limit on the number of new staff assigned for mentoring if the team is still to get the work done.

Overview of training tools available

Technology can also enhance the efficiency of the training process, especially if it is used in such a way as to support the principles of adult learning previously described (Kruse and Keil, 2000). Additionally, today’s technology supports distance learning, which means huge cost savings can be realized because employees do not have to travel to receive training. Below are brief descriptions of some of the technical tools available, along with references that provide additional detail.

**Computer-based training modules**

Computer-based training (CBT) modules can be used wherever a computer is available, and can be distributed as a file by e-mail or loaded onto the computer by diskette or CD. CBT modules are self-paced, provide specific and immediate feedback, and can be hyper-linked with other resource documents. Additionally, CBT modules can be designed so that they are self-scoring, and so that they provide documentation of proficiency through a file that verifies a passing score was achieved on the tests incorporated into the material. Once loaded onto a computer, they can be revisited as needed to reinforce the initial training. CBT modules can be easily updated and reissued as needed. In the pharmaceutical industry, this methodology is frequently used to teach product information to the sales force, but it has also been applied to drug safety (Benson et al. 1999). However, CBT modules are not truly interactive, since additional support must be provided for the user to be able to ask questions or seek clarification.

**The ‘virtual’ classroom**

Since teleconferences do not allow discussion of visual material and CBT courses are not interactive, many are now leveraging video-conferencing capabilities to support distance learning. New tools allow instructors to control presentations using synchronized multimedia, share applications with the audience, provide electronic ‘hand-raising’ for questions, and acquire a screen capture of any student’s desktop via a ‘glimpse’ feature. These tools are expensive, and without high-speed connectivity they can be cumbersome and slow during use, even more so when a large number of users are participating. This is especially problematic with international audiences, even if dedicated lines are available between sites (Anonymous, 2001).
Web-based learning

This approach attempts to bypass many of the limitations of video-conferencing by utilizing the Internet as the mode of transmission. The same methods may also be applied to internal company ‘intranets’. Using a Web site for distance learning eliminates many of the technical limitations of video-conferencing while still providing interactivity, and, perhaps most importantly, allows for simulations to teach complex performance skills (Driscoll, 1998). Well-designed Web sites can result in very efficient training programs that, in some situations, have achieved results comparable to instructor-led training in 40 to 60 per cent less time. However, such success is dependent on a computer-literate audience and internal systems that enable delivery of robust programmes. And, whereas instructor-led sessions remove participants from their daily work so that they can focus on learning, there is no such protection in this environment (Zenger and Uehlein, 2001).

External partners in the case-handling process

Introduction

Pharmaceutical companies routinely hire CROs to perform all or portions of work formerly done by internal company personnel. Although companies have traditionally hired CROs to monitor clinical trials, CROs are now expanding their capabilities. There are now some CROs who can perform almost any function, including, but not limited to, data management, statistical analysis, medical writing, publishing, etc. Additionally, some CROs now offer a full menu of services normally performed by a safety department, from collection of reports (through call centres as well as other avenues), entering reports into a database, medical review, and even submitting reports to regulators. This menu of safety services is not even limited to case handling; CROs are now offering safety surveillance services as well (Doan, 2000).

There are certainly pros and cons to utilizing a CRO rather than internal company personnel for any portion of work. However, discussion of these is outside the remit of this chapter. What this section will attempt to provide are some basic principles for partnering successfully with a CRO when at least a portion of the safety work has been out-sourced to them. Additionally, the end of the section will discuss other types of external partner that may be used for safety work.

Clinical research organizations

It is to the company’s advantage for the CRO to be able to perform as efficiently as possible. One key way to encourage this is to minimize the deviations the CRO is required to make from its own internal SOPs and guidelines. Part of the routine CRO selection process should include a review of all relevant SOPs and guidelines used by the CRO. Company reviewers can then not only ascertain what candidate CROs have the closest fit with the company, but the quality of these documents will provide insight as to the quality of the CRO itself.

Once the selection is made, a further in-depth analysis of differences between company and CRO SOPs should be made to identify potential areas of conflict, clarify marginal areas and agree on what deviations should be made. In many instances, subtle differences may have little impact to the work. It is best if this detailed review is performed together by
knowledgeable content experts from both sides, preferably persons who will be directly involved in the out-sourced work. For example, if the out-sourced work involves safety reporting in a clinical trial, then members from the CRO safety group and the company clinical trial safety group should establish contact as early as possible to agree upon the case-handling flow for the trial. Monitors and other clinical team members should be involved in this discussion as well. Company representatives should be open to suggestions from the CRO, since they may have valuable insight about best practices from their experiences in working with other companies.

In addition to workflow, the roles and responsibilities should be clearly defined. The CRO should provide documentation to the company that their personnel are qualified to perform the services delegated to them. For example, if the CRO is providing medical review of case reports, then they should provide proof that the reviewing CRO physician meets the same standards set for internal company physicians who perform this work. Additionally, it is often helpful to have a person appointed as primary point of contact both within the CRO and within the company safety department. This ensures efficiency in communication and issue resolution. Since CROs frequently have a high rate of staff turnover, it is also reasonable for the company to require that the CRO is accountable for the transition of legacy knowledge and training replacement personnel.

In a clinical trial situation, it is also helpful for the CRO to generate a safety-reporting plan for the study, reiterating agreements on definitions, roles, accountabilities, and to include a diagram of the agreed workflow. Such a safety reporting plan will not only uncover possible misunderstandings before the trial begins, but it will also serve as a resource for new team members (for the CRO as well as the company), and may be used as a reference point in resolving future confusion. It is critical that any changes to the original plan are incorporated into the document, and that revisions are reviewed by all involved.

One key component of the safety reporting plan for a clinical study is an efficient process for tracking queries and query resolution. This should be agreed in conjunction with data management and other relevant members of the clinical team who participate in these efforts, and roles and accountabilities should be clearly defined. Plans should include a method of continuous and ongoing data comparison and corrections between the safety and clinical databases, in order to minimize the time at the end of the study needed to declare clean file for the study and lock the trial database. Furthermore, reconciliation between the safety and clinical databases should be limited to key fields, as 100 per cent agreement between the two can never be achieved, due to the fact that the safety data reflects a point in time (i.e. the time around the occurrence of the serious AE) and the clinical data reflects a continuum of visit-based data that changes over the course of the trial.

It is also important that areas of the company, such as the safety department, who are working with the CRO are able to provide feedback to the ‘owner’ of the contract on CRO performance. This feedback should be as real-time as possible, so that issues can be addressed quickly. For example, the safety department should notify a clinical team who is utilizing a CRO for monitoring a study if the CRO is not adhering to reporting timelines, if the quality of the reports provided is poor, and if queries are not answered in a timely manner. It is much easier to deal with poor performance with a CRO if expectations and requirements are outlined clearly in the contract itself – otherwise it may be very difficult to hold the CRO accountable. Owing to the critical nature of safety reporting, it may be useful to have an addendum to the contract or a portion of the contract itself that outlines specific
safety requirements. Some companies go so far as to include automatic monetary penalties if these requirements are not met.

Other external partners

Other than CROs, there are a variety of external partners that may also be utilized by safety departments. Examples of these are temporary data-entry personnel, technical consultants and vendors contracted for document management. Regardless of function, it should be remembered that regulatory requirements for these company agents are the same as for a company employee. The same components (SOPs, training records, etc.) are subject to audit, and regulatory authorities expect that proper controls be in place to ensure system security and data integrity. Documentation is key, preferably within a contract that specifies the work to be performed.

Case distribution to external parties other than regulatory authorities

Introduction

In addition to regulatory authorities, companies frequently need to communicate safety information to parties other than regulators (in some situations, this dissemination of information may be requested or even mandated by regulators). The key to any effective safety communication is to ensure that the right message is sent to the right audience in the right way at the right time. This section will describe the methods used with three important audiences:

- data monitoring committees (DMCs)
- investigators
- health care professionals.

Data monitoring committees

As defined in the ICH E9 guideline, (ICH, 1998), a study sponsor may establish a DMC, to assess critical efficacy and safety data variables at intervals during the course of a clinical study in order to recommend to the sponsor whether to continue, modify or terminate the study. A DMC may either be a group of experts independent from the sponsor and from the investigators of a clinical trial, or may consist of internal experts from the sponsor organization. Because of the risk of compromising study integrity, it is highly desirable to have individuals who are not members of the clinical team conducting the study to monitor the incoming data.

Use of a DMC should be considered when the primary outcome of the study is a serious AE other than death, if there is a potential for short- and long-term risks to the subjects (especially if trial procedures are themselves risky or inconvenient for the subject), or when there is an alternative treatment available for the condition under study. DMCs are particularly helpful in Phase III trials that are large, multi-centre, long duration, randomized, and double-blinded, that have death as an endpoint, or are conducted in patients with a high
intrinsic mortality risk. DMCs may also be useful in an earlier phase trial when the subjects are unable to give informed consent or when a new chemical entity is likely to cause serious AEs.

When study endpoints are also serious AEs, a regulatory authority waiver releasing the sponsor from expedited reporting of these endpoints is highly desirable to protect study integrity, since, unless prior arrangements are made, authorities expect expedited reports to be unblinded prior to submission. Most authorities will grant such waivers if a DMC is in place to monitor the safety of study subjects. The DMC evaluates safety in an ongoing trial through an overview of relevant points in the data flow. Responsibilities of the DMC regarding safety include:

- ensuring the safety of subjects participating in the study;
- reviewing interim reports for evidence of adverse treatment effects;
- recommending changes in the protocol to improve subject safety;
- providing advice on operational procedures affecting subject safety.

The DMC may also be charged with recommending early termination of the study for safety reasons. According to ICH E9 (ICH, 1998), the goal of any interim analysis should be to stop the study early if unacceptable adverse effects are apparent. Stopping rules must be clearly defined and understood by the DMC and the sponsor. Typically, stopping early for safety reasons does not require the same level of proof as stopping for efficacy, as it is not necessary to prove harm.

Most DMCs review, at a minimum, serious AE reports from the study, both at a single case level and/or in a summary fashion. The DMC charter should specify the format and frequency of safety reports sent to the DMC, as well as who will provide it (e.g. the safety department or clinical team) and the source of the data (e.g. the safety database or the clinical database). In a large company, there may be multiple large DMC-monitored trials in progress at once, so the workload of providing safety data at frequent intervals can be significant. In order to minimize the resource required for this, it may be helpful for the safety department to program a detailed individual case report suitable for distribution to an external group (e.g. with the patient identifiers encrypted to maintain confidentiality), as well as a standard DMC summary report that contains all of the key fields needed.

**Investigators**

The US FDA requires that a company conducting clinical trials under a US Investigational New Drug Application (IND) must submit expedited written IND safety reports to FDA and all participating investigators any time it receives information on adverse experiences associated with the use of the drug that are serious, unexpected, and possibly related to the drug under study (see Chapter 9). The regulations specifically require that these IND safety reports:

- contain the same content, whether sent to the FDA or investigators
be sent to both the FDA and all investigators within 15 calendar days from the time that
the company becomes aware of the event

identify all safety reports previously submitted to the IND concerning a similar adverse
experience

analyze the significance of the adverse experience in light of previous, similar reports

IND safety reports sent to investigators are commonly known as ‘investigator safety letters’
(ISLs). The GCP guideline (ICH, 1997) requires investigators to communicate ISL information
to their IRB or IEC according to the time frame specified by the IRB or IEC, and
maintain evidence of this communication as well as copies of all ISLs received in their study
file. These documents are subject to audit, both by company monitors and by regulatory
inspectors.

Benchmarking data collected from major pharmaceutical companies regarding their ISL
practices indicate that methods vary widely in terms of format: some simply send the
investigators a copy of the MedWatch or CIOMS regulatory report sent to the FDA, others
send a narrative summary description, with or without an attached line listing, and others
send a custom report that incorporates single case as well as summary data. Although
sending a copy of the regulatory report form is the easiest and quickest way to ensure that
investigators receive the same information as the FDA, investigators frequently complain
that the formats are not user friendly or concise, are difficult to interpret, and result in
additional paper to manage. Narrative summaries, while better received by the investigators,
tend to drift easily into subjective interpretation and may omit key information present in
the more rigorous format of a structured report. Line listings end up being a data dump
without the analysis and synthesis needed to make the information meaningful to the
recipient.

The most successful solution appears to be a customized report that contains all of the
same information contained in the regulatory report, but in a more user-friendly, concise
format. However, since this approach has become an industry trend, investigators are now
faced with interpreting a different type of report from each company (some companies even
use different reports for different therapeutic areas), each attempting to provide the same
basic information. Adoption of an industry standard would improve the quality of this
important risk communication. It is expected that a recommendation for a standard will be
made by the CIOMS VI working group.

It is a common misconception that ISLs can be considered as updates to the Investigator’s
Brochure (IB). The FDA has clarified that although the investigator letter may be attached to
the IB as an informational update, additional cases of the same event(s) should still be
regarded as unexpected (and submitted as expedited IND safety reports and ISLs) until the
new ADR is added to the core safety information section of the IB. Once it is added, the
revised, updated IB can be sent to all investigators as an official modification.

Studies not conducted under a US IND are subject to ICH guidelines that require study
sponsors to keep investigators and IRBs/IECs informed of new safety information during
the course of a clinical study. The method, format, and time frame for this are currently not
specified. Guidances supporting the new EU Clinical Trial Directives are expected to
provide more structure around this activity (see Chapter 9).
Dear Doctor (Healthcare Professional) letters

Although the term ‘Dear Doctor’ letter is often used interchangeably with the letters sent to investigators during a clinical trial (referred to above as ISLs), the two are not synonymous. ‘Dear Doctor’ letters, now known as ‘Dear Healthcare Professional’ (HCP) letters to indicate the broader target audience of pharmacists, nurses and others involved in patient care, are used to communicate important safety information in the post-marketing environment rather than solely within the confines of a clinical study. This mechanism is used as an expeditious way to highlight important safety information to those who prescribe and/or dispense and/or administer medications while other measures, such as revision of drug labels and packaging, are under way. The company may take this action voluntarily or be required to do so by a regulator. Regulators have also issued these letters independent of the company. It is to the company’s advantage to participate in generating the letter in order to have some influence on the language it contains. There is also a public relations advantage to being perceived as proactive in risk communication. Chapter 8 provides a model for the essential elements that should be contained in this written communication.

Typically, the HCP recipients of these letters are generated from customer lists held by sales and marketing, professional society membership rosters, hospital employment databases, licensure registries, and even telephone directories. Companies may also pay for full-page displays of the letter in journals and other publications that target HCP audiences. These letters are also posted on company and professional Web sites, as well as the Web sites of the FDA and other regulators. When issuing a letter, it is very important to ensure simultaneous notification to regulators in all countries where the drug is marketed. Regulators monitor each other’s Web sites closely, and are not pleased when companies do not inform them directly of safety issues known to other agencies.

The type of information contained in Dear HCP Letters may be categorized broadly into three types:

- **New ADRs.** When a company strongly suspects or confirms that a drug causes an ADR that is currently not described in the prescribing information, the company has a legal ‘duty to warn’ about this discovery quickly.

- **Notification of increased severity of ADRs.** The most severe types of ADR are usually not seen until population exposure has exceeded many thousands of patients. This includes more severe forms of known ADRs. One common example of this is drug-induced hepatotoxicity, which may have only been seen as ‘elevated liver enzymes’ in clinical trials, but which after market approval may result in drug-induced hepatitis, or hepatic necrosis, resulting either in the need for a liver transplant or in death.

- **Reiteration of contraindications, warnings, etc.** The company may learn that a drug is being prescribed or used in a way that increases risk to patients. Examples include co-prescribing with potentially interacting drugs, exceeding safe dosages or durations, and use in sensitive or prohibited populations (pregnant women, diabetics, etc.). Even if this information is contained in the current prescribing information, the company has an ethical obligation to re-emphasize the dangers to the public, and the Dear HCP letter may be used as one avenue of doing so.
Since the type of information described above can be complex, it was thought that communicating this type of information only to HCPs would minimize public alarm while ensuring patient safety, consistent with the concept of the intervention of ‘the learned intermediary’. Today, with the technical savvy of consumer advocacy and watchdog groups, as well as lawyers and the media, publication of a Dear HCP letter frequently makes headlines in both television and the newspapers. Proponents of this wider dissemination point out that increased awareness will increase the potential for protecting patients. However, the increased publicity may also lead to unintended adverse consequences due to misinterpretation of the information, such as needless patient anxiety and potentially dangerous patient actions, such as abrupt discontinuation prior to physician consultation.

Conclusion: Vision for the future

The CIOMS 1A Working Group (CIOMS, 1994) put forth a vision (recently reiterated by the CIOMS V Working Group in its 2001 report (CIOMS, 2001)) that the interest of public health could best be served by having a single database with worldwide access, where AE cases would be entered only once, regardless of source. Until this vision is realized, even with the advent of electronic ADR submissions to regulators, safety reporting will continue to result in duplication of effort, with the danger of double counting and misinterpretation. Additionally, although considerable progress has been made over the past decade in achieving harmonization for many aspects of drug safety surveillance and reporting, much remains to be done in order to eliminate unnecessary regulatory differences and inefficiencies that consume resources and time but add little real value to pharmacovigilance.

Removal of such technical and regulatory obstacles would have a profound impact on the functional aspects of drug safety departments in pharmaceutical companies, not only in terms of organization and processes, but also in terms of the types of skill needed and work done. The majority of resources in drug safety departments could be shifted away from administrative activities, allowing increased focus on scientific analysis and medical evaluation, thus leading to enhanced public health protection through better assurance of the safety of medicinal products.

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References


Further reading