Regulatory Aspects of Pharmacovigilance

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Introduction

Pharmaceutical companies have a responsibility to make the use of their medicines as effective and as safe as possible. Hence, companies need to conduct effective pharmacovigilance throughout the life cycle of all medicinal products, so that accurate, well-informed and up-to-date information is provided to physicians, pharmacists and patients. In addition, companies must keep regulatory authorities informed with regard to the ongoing safety profiles of their products so that the authorities can fulfil their own obligations to protect public health.

Each company should collect safety data on all of its products, from all available sources on a worldwide basis, and have appropriate evaluation and reporting mechanisms in place. However, the current diversity of regulatory requirements for reporting adverse drug reactions (ADRs) results in different authorities requesting that information from the same source be presented according to different inclusion criteria, formats and time intervals. Despite the best efforts of the Council for International Organizations of Medical Sciences (CIOMS) and the International Conference on Harmonization (ICH), it is evident that effort put into compliance with diverse ADR reporting requirements draws resources away from the medical evaluation of safety signals. Thus, a single set of standards for the worldwide communication of safety information is still required in order to facilitate a shift in emphasis away from the administration of safety data towards more cost-effective identification and evaluation of important safety signals.

Council for International Organizations of Medical Sciences

CIOMS is a non-governmental organization established in 1949 by the World Health Organization (WHO) and the United Nations Educational, Scientific and Cultural Organization (UNESCO), primarily to act as a forum for capturing and disseminating opinion on new
developments in biology and medicine, as well as in exploring their social, ethical, moral, administrative and legal implications.

In 1986, CIOMS initiated the ‘CIOMS I’ Working Group with the objective of standardizing expedited ADR reporting requirements. Subsequent CIOMS working groups have addressed a variety of safety-related topics, as follows:

I International reporting of adverse drug reactions
Ia Harmonization of data elements for electronic ADR reporting
II International reporting of periodic drug-safety update summaries
III Guidelines for preparing core clinical-safety information on drugs
IV Benefit–risk balance for marketed drugs: evaluating safety signals
V Current challenges in pharmacovigilance: pragmatic approaches
VI Safety monitoring and evaluation during clinical trials.

Groups I–V have completed their activities and, with the exception of CIOMS Ia, have published their recommendations as CIOMS reports; CIOMS VI activities are ongoing. Each CIOMS Working Group report represents a significant milestone in pharmacovigilance. Groups I, II and V have contributed significantly to the harmonization of international ADR reporting requirements, and are described further below.

CIOMS I – International reporting of adverse drug reactions

The CIOMS I group was formed with the objective of developing an internationally acceptable method for manufacturers to report post-marketing ADRs rapidly and effectively to regulatory authorities. The group comprised individuals from regulatory authorities and pharmaceutical companies and issued its final report in 1990.

The group established the principle that serious, medically substantiated, unexpected ADRs should be regarded as the most important source of safety signals in marketed products, thereby warranting expedited data collection, evaluation and notification to authorities. This principle has survived reasonably well as international harmonization of reporting requirements has progressed, albeit with resistance to acceptance by some authorities.

The final report of the CIOMS I group contains several recommendations relating to conventions and definitions, report content and format. In due course, this established the CIOMS I form for worldwide expedited reporting.

Conventions presented by the CIOMS I group that have been carried forward into many ADR reporting regulations worldwide, include:

- A ‘suspected reaction’ means that a physician or other healthcare professional has judged it a reasonable possibility that an observed clinical occurrence has been caused by a drug.

- CIOMS reports are not required for ‘events’ or ‘experiences’ where causal judgement
has not been made; the exception to this rule relates to spontaneous reports, which should always be regarded as suspected reactions.

- Companies should take local prescribing texts into account when determining whether a serious ADR is ‘expected’ or not for expedited reporting purposes.

- Recognizing that initial notifications of ADRs to pharmaceutical companies are often lacking in detailed information, CIOMS reports should be filed once they contain the following minimum standard of information:
  - an identifiable source
  - a specific patient
  - a suspected drug
  - a suspected reaction.

- Manufacturers should submit completed CIOMS I forms to regulatory authorities within 15 working days after initial receipt of information, thereby allowing companies sufficient time to collect reasonably detailed information on a case before notification and reducing the need for follow-up reports. Unfortunately, this concept has not survived intact, with regulatory authorities generally requiring expedited reports within 15 calendar days.

- The ‘regulatory clock’ should start once the company, or any part or affiliate of a company, receives sufficient information to qualify as a CIOMS report.

CIOMS II – International reporting of periodic drug-safety update summaries

The CIOMS II Working Group was convened with the objective of developing a model periodic safety update report (PSUR) that could serve as the basis for harmonizing international approaches to periodic reporting, and it issued its final report in 1992.

The CIOMS II Working Group established well-recognized standards for PSURs that have progressed through the European Union (EU) and ICH processes dealing with this topic. Although the CIOMS II recommendations have been superseded by the report format and content recommended in the ICH E2C guideline on this topic, the following principles established by the CIOMS II group merit recognition:

- PSURs should provide a critical review of safety information accumulated from various sources since the time of the previous review, and put this information into context against the earlier information.

- Each regulatory authority requiring a safety update should receive the same PSUR simultaneously.

- PSURs should represent routine compilations of safety information, so that both manufacturers and regulators can be reassured that pertinent safety data have been reviewed in a systematic manner.
- Cumulative data should only be required to place issues into context.

- PSURs should be based upon the drug substance under review and should include combination products, with reference to the active moiety; it may also be appropriate to differentiate formulations, routes of administration and indications within the same report.

- The timing of PSURs should be based on the international birth date (IDB), i.e. the date of first approval by a regulatory authority; the manufacturer's safety database should then be locked at six-monthly intervals thereafter, creating a series of 'official' data lock points.

- A cumulative series of six-monthly updates should suffice to meet the needs of those regulatory authorities that require annual, biennial or five-yearly PSURs.

In addition, the CIOMS II final report contains a useful example PSUR, containing an evaluation of two fictitious safety issues that arose during the period under review, evidently based on a 'real-life' situation and produced by an experienced drug safety organization. This example illustrated very well the level of critical evaluation that a company could reasonably apply during the production of a PSUR, and it is still relevant to this day when complying with global PSUR requirements.

**CIOMS V – Current challenges in pharmacovigilance: pragmatic approaches**

The CIOMS V Working Group was convened to consider practical proposals on a wide range of issues concerning pharmacovigilance and ADR reporting, including unresolved issues from previous CIOMS Working Groups, and it issued its final report in 2001.

Topics covered by the report include:

- Sources of individual case reports
  - consumer reports
  - published literature
  - the Internet
  - solicited reports
  - aspects of clinical trial reports
  - epidemiology – observational studies and use of secondary databases
  - disease-specific registries and regulatory ADR databases
  - licensor–licensee interactions

- Good case management practices
  - clinical evaluation of cases
  - assessing patient and reporter identifiability
– criteria for assessments of seriousness and expectedness
– case follow-up
– narrative summaries

• Good summary reporting practices
  – PSUR content
  – frequency and timing of reporting
  – miscellaneous proposals for managing PSURs

• Determination and use of population exposure data
  – PSURs and exposure data sources
  – technical considerations
  – spontaneous reporting and patient exposure
  – examples of denominator determination and use
  – patient-exposure and measurements of risk

• Clinical safety reporting regulations
  – overview of current regulations
  – recommendations for change

Although only recommendations, it is evident that many of the proposals within this report will be considered under the ICH process and/or incorporated into local regulations. In addition, many companies have chosen to adopt several of the recommendations into daily working practice without the need for regulation to occur in support.

The International Conference on Harmonization

Origin and objectives

The ICH is a unique project bringing together regulatory authorities from three regions (EU, USA and Japan) with experts from the pharmaceutical industry. The process involves discussion of scientific and technical aspects of product registration, leading to recommendations that facilitate harmonization of requirements for product registration, thereby reducing the need to duplicate effort during the development of new medicinal products.

The terms of reference of the ICH were defined as follows:

• Provide a forum for constructive dialogue between regulatory authorities and the pharmaceutical industry regarding differences in the technical requirements for product registration in the EU, USA and Japan.

• Identify areas where modifications in technical requirements or greater mutual
acceptance of R&D procedures could lead to more economical use of resources without compromising safety.

- Recommend practical ways to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for registration.

Co-sponsors of the ICH are:

- European Commission (EC)
- European Federation of Pharmaceutical Industries and Associations (EFPIA)
- Ministry of Health, Labour and Welfare (MHLW), Japan
- Japan Pharmaceutical Manufacturers Association (JPMA)
- Food and Drug Administration (FDA), USA
- Pharmaceutical Research and Manufacturers of America (PhRMA).

In addition, the International Federation of Pharmaceutical Manufacturers’ Associations (IFPMA) provides the ICH secretariat, and the WHO, European Free Trade Association and Canada have provided observers to the process.

Five ICH conferences have taken place to date:

- ICH1 November 1991, Brussels
- ICH2 October 1993, Orlando
- ICH3 November 1995, Yokohama
- ICH4 July 1997, Brussels
- ICH5 November 2000, San Diego.

The ICH6 meeting is scheduled for November 2003 in Osaka, Japan.

Clinical drug safety-related topics have been addressed at several ICH meetings, primarily in association with expedited and periodic reporting requirements as well as developing standards for the electronic communication of clinical safety data. Recently, the ICH Steering Committee initiated a second phase of drug safety-related activities at a meeting in Brussels (February 2002). Topics being considered under this phase include:

- An addendum to the E2C (PSUR) guideline
- ICH E2D – Post-approval Safety Data Management: Definitions and Standards for Expedited Reporting
- ICH E2E – Pharmacovigilance Planning

The addendum to ICH E2C has been completed and is now considered part of the ICH E2C guideline. At the time of writing, the E2D and E2E guidelines are in development and, hence, are not considered further.
The International Conference on Harmonization process

Expert working groups (EWGs), containing experts from each of the six ICH co-sponsors, provide technical advice to the ICH Steering Committee with regards to harmonization topics, with the objective of producing a guideline on their respective topic that then forms the basis for implementation within each ICH region. Each guideline passes through five stages (‘Steps’) from original selection of the topic through to legislated implementation:

Step 1 Selection of topic, preliminary discussions and preparation of a draft guideline
Step 2 Formal consultation with stakeholder organizations
Step 3 Consolidation of comments and preparation of a revised draft guideline
Step 4 Endorsement of the final draft by the ICH Steering Committee and ‘sign-off’ by the co-sponsors
Step 5 Incorporation into domestic regulations or other administrative procedures.

To date, there have been three ‘Clinical Safety Data Management’ EWGs addressing the following topics:

- E2A Definitions and standards for expedited reporting
- E2B Data elements for transmission of individual case safety reports (ICSRs)
- E2C PSURs for marketed drugs.

In addition, the ICH E1 guideline (Population exposure) defines the extent of population exposure needed to assess clinical safety during development of a new product and the ICH E6 Guideline (Good clinical practice) specifies some obligations relating to safety reporting during the conduct of clinical trials.

Two ‘multidisciplinary’ topics had clinical safety as one of their components, ICH M1 (Medical terminology for regulatory purposes) and ICH M2 (Electronic standards for the transfer of regulatory information and data). These topics were addressed by working parties, which then produced standards for adoption rather than specific guidelines.

International Conference on Harmonization definitions

Adverse event

The E2A and E6 guidelines indicate that an adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, and which does not necessarily have to have a causal relationship with this treatment.

Hence, an AE can be any unfavourable or unintended symptom, sign, laboratory parameter or disease entity temporally associated with the use of a medicinal product, regardless of any causality assessment by either the reporting healthcare professional or company physician.
Adverse drug reaction

In the context of clinical investigations, the E2A guideline indicates that all noxious and unintended responses to a medicinal product relating to any dose should be considered as suspected ADRs.

The guideline signifies that the phrase ‘responses to a medicinal product’ means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility. However, it then confuses matters by also indicating that an AE should be considered as an ADR if ‘the relationship cannot be ruled out’. This leaves regulatory authorities and companies to interpret the definition of an ADR, for example:

- an AE could be considered an ADR if it is not possible to exclude totally that a causal relationship exists; or
- there needs to be a plausible reason as to why a causal relationship might exist for an AE to be considered as an ADR.

The first (more conservative) interpretation would mean that almost any AE having a temporal relationship to administration of an investigational product (i.e. virtually all of them) could be considered as an ADR. However, the second interpretation has further support within Section III.A.1 of the E2A guideline, which indicates that:

- all cases judged by either the reporting healthcare professional or the sponsor as having a reasonable suspected causal relationship to the medicinal product qualify as ADRs;
- the expression ‘reasonable causal relationship’ is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

Regarding marketed products, the E2A and E6 guidelines both restate the WHO definition, indicating that an ADR is a response to a drug that is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or for modification of physiological function.

Spontaneous reports are defined within the E2C guideline as any unsolicited communications to a company, regulatory authority or other organization that describe ADRs in patients and which do not derive from a clinical study or other organized data collection scheme. The E2A and E2C guidelines indicate that spontaneous reports from consumers or healthcare professionals should all be regarded as suspected ADRs. In contrast, guidance is lacking as to when a literature report qualifies as a suspected ADR.

Serious adverse event/adverse drug reaction

ICH E2A and E6 define an AE (or ADR) as serious if it:

- results in death
- is life threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
• results in persistent or significant disability or incapacity
• is a congenital anomaly or birth defect.

In addition, the E2A guideline introduced the concept of ‘medically important’ AEs that should also be regarded as ‘serious’ even if they do not meet any of the above criteria (see below).

**Death** The ICH guidelines do not provide specific guidance on the interpretation of the criterion ‘results in death’, thereby leaving it open to interpretation by companies and regulators. For example, death is usually the outcome of an event that causes it and, in general, the cause of death would be regarded as the AE; one exception is ‘sudden death’, which should usually be regarded as the AE and ‘fatal’ as its reason for being ‘serious’. In some countries (e.g. Germany and Sweden), the term ‘unexplained death’ may also be reported as a specific event, whereas in the USA all reports of death should be submitted to the FDA, even if the cause of death (i.e. the underlying AE) is unknown.

**Life threatening** The term ‘life threatening’ refers to an event where the patient was at *immediate* risk of death at the time of the event, not an event that might have caused death had it been more severe. For example, although pulmonary embolism has the potential of being life threatening in some circumstances, it should only be considered ‘life threatening’ if it was so severe in intensity that there was an immediate risk of the patient dying from the pulmonary embolism.

**Hospitalization** The term ‘hospitalization’ refers to the situation when an AE is associated with an unscheduled admission into hospital, for the purpose of investigating and/or treating the AE. For example, when administration of a drug results in thrombocytopenia, which then necessitates an overnight admission for bone marrow biopsy and platelet transfusion.

Usually, hospitalization that occurs on an elective basis should not be regarded as a serious AE. For example, when a patient is admitted into hospital for a scheduled cholecystectomy, for the treatment of pre-existing cholelithiasis, this would usually not be regarded as an AE *per se* and the fact that the patient is hospitalized is irrelevant. However, if the patient suffers an unexpected deterioration in their condition (e.g. development of acute cholecystitis) that requires hospitalization for urgent cholecystectomy, then a serious AE has occurred, even if it was considered unrelated to the drug therapy.

Further interpretation is required when the local medical environment is considered. The practice within many pharmaceutical companies is to consider any hospital stay exceeding 24 h as ‘hospitalization’.

**Disability or incapacity** The term ‘persistent or significant disability’ is open to interpretation and requires judgement. In general, it should be regarded as any situation where an AE has a clinically important effect on the patient’s physical or psychological well being, to the extent that the patient is unable to function normally.

**Congenital anomaly** Any congenital anomaly observed in a child should be regarded as a ‘serious AE’ when the mother (or father) was exposed to a medicinal product at any stage during conception or pregnancy.
Medically important adverse events ICH E2A introduced the concept of ‘medically important’ AEs, which may also be known by the phrase ‘required medical intervention’. The two terms should be regarded as synonymous, as both refer to events of clinical significance that might otherwise not be considered as serious if the other criteria are used but yet they may jeopardise the patient’s health such that medical intervention is required to prevent one or more of the ‘serious’ outcomes. These situations should usually be regarded as ‘serious’, both in a clinical and a regulatory sense — this emphasizes that the determination of ‘seriousness’ should be a matter of clinical judgement rather than regulatory ‘box ticking’.

For example, this might apply in a situation where a patient requires treatment in an emergency room for allergic bronchospasm but is not formally admitted, as such patients can be discharged home on a same-day basis. Other examples cited in the E2A guideline that should usually be considered as serious are blood dyscrasia or convulsions that do not result in hospitalization or development of drug dependency or drug abuse.

Unexpected adverse event/adverse drug reaction

ICH E2A and E6 indicate that an adverse reaction should be regarded as ‘unexpected’ if its nature or severity is not consistent with information in the relevant source documents, namely the company’s Investigator’s Brochure (IB) (investigational products) or local prescribing information texts (marketed products).

Reports that add significant information on the specificity or severity of a known ADR may also be considered as unexpected events, for example:

- a report of interstitial nephritis for a product that has a recognized association with acute renal failure;
- a report of fulminant hepatitis for a product that has hepatitis as a labelled ADR.

Unlisted adverse event/adverse drug reaction

An unlisted ADR is one whose nature, severity, specificity or outcome is not consistent with the information included in the ‘Company Core Safety Information’, itself a section of the company’s core prescribing information text.

Although similar to the above definition of ‘unexpected’, the E2C guideline introduced the concept of ‘unlisted’ ADRs specifically for periodic reporting purposes. Hence, whereas ‘unexpectedness’ should be based on the relevant local prescribing text or IB and used for expedited reporting purposes, ‘listedness’ should be based on the company’s ‘core’ prescribing text(s) and used only for periodic safety reporting purposes.

ICH E2A – Clinical safety data management: definitions and standards for expedited reporting

The E2A EWG was created to develop standards for the issue of expedited reports for development products. The resultant guideline reached Step 4 in October 1994 and has since been implemented, to a greater or lesser extent, within all three ICH regions.

The E2A guideline defines expedited reporting requirements for all ADRs relating to products under clinical investigation, including the investigation of new formulations or
indications for products already on the market. The fundamental principle is that serious unexpected ADRs warrant expedited reporting to regulatory authorities, provided that they meet minimum criteria for reporting and include a causality assessment. This includes reports from the following sources:

- any clinical or epidemiological investigation, regardless of design or purpose
- post-marketing use
- published literature
- ADR registries generated by regulatory authorities.

In contrast, the E2A guideline indicates that expedited reports should not be necessary for:

- serious expected ADRs
- serious AEs from clinical investigations, which have been considered as unrelated to the study drug
- non-serious ADRs.

**Reporting requirements**

The ICH E2A expedited reporting requirements are summarized in Table 9.1.

<table>
<thead>
<tr>
<th>Report</th>
<th>ADR type</th>
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<tbody>
<tr>
<td>7-day</td>
<td>Fatal or life-threatening unexpected</td>
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<tr>
<td>15-day</td>
<td>Serious unexpected</td>
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With regard to fatal or life-threatening unexpected ADRs, the sponsor should notify regulatory authorities as soon as possible, but no later than seven calendar days after first knowledge that a case qualifies. The initial notification may be made by telephone, facsimile or in writing. Within a further eight calendar days, each initial notification should be followed by a complete report, including relevant previous experience with the same or similar medicinal products and an assessment of the importance and implications of the findings. Other serious unexpected ADRs should be notified as soon as possible, but no later than 15 calendar days after first knowledge by the sponsor that the case meets the minimum criteria for reporting.

With regard to informing investigators, Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs), the E2A guideline simply cross-refers to the ICH E6 guideline that discusses the need to provide new safety information to such parties (see below).

**Minimum criteria for reporting**

However a case report is submitted for expedited reporting, Attachment 1 of the E2A guideline details the data elements that should be included within a report:
In many instances, the information required for a final description and evaluation of a case report may not be available within the stipulated time frames for expedited reporting. Thus, the guideline indicates that initial reports should be submitted within the specified time frames provided that the following minimum criteria are met:

- an identifiable patient
- a suspected medicinal product
- an identifiable reporting source
- an event or outcome that can be identified as serious and unexpected
- a reasonable suspected causal relationship (for cases arising from clinical investigations).

Although a submitted case report may satisfy only these criteria, the sponsor of the clinical investigation is still obliged to seek follow-up information on the case and submit this as it becomes available.

**Causality assessments**

ICH E2A indicates that formal causality assessments are required for case reports arising from clinical investigations: all cases considered by either the reporting investigator or the sponsor as having a reasonable possibility of a causal relationship to the study drug qualify as suspected ADRs.

At present, a standard international nomenclature to describe causal relationships is lacking. As a result, pharmaceutical companies vary in their approach to causality (see Chapter 4). Several companies have opted to consider an AE as either ‘suspected’ or ‘not suspected’, in accordance with the concept that the phrase ‘reasonable causal relationship’ means that there are facts, evidence or other reasons to suggest a causal relationship. These companies then simply oblige their investigators to answer only ‘Yes’ or ‘No’ to an appropriately phrased question on causality.

**Post-study events**

When patients experience serious AEs after completion of their participation in a clinical trial and they report these events to the investigators that had cared for them, the E2A guideline advises that these reports should be considered as though they were study reports,
even though they may not be entered onto the clinical trials database itself. Hence, for safety data management purposes, they still need causality assessments and a determination of expectedness.

**Managing ‘blinded’ therapy cases**

In the event that an ADR arises from a ‘blind’ clinical study, ICH E2A provides a lengthy consideration of the need to break the ‘blind’ for expedited reporting purposes. Although it is advantageous to retain the ‘blind’ for all patients prior to final study analysis, the E2A EWG recognized that breaking the ‘blind’ for a single patient usually has little or no implications for the conduct of the study or analysis of the final data. Hence, the guideline recommends that the ‘blind’ should be broken for individual cases that qualify for expedited reporting, although it should still be maintained for the individuals responsible for the analysis and interpretation of study results.

The guideline provides one exception to this rule. When a fatal or other serious outcome is the primary efficacy endpoint in a clinical trial, it is possible that the statistical integrity of the investigation may be compromised if the ‘blind’ is broken in advance of the final study analysis. In this instance, the guideline advises companies to reach agreement with regulatory authorities that such events should be treated as disease-related and not be subject to routine expedited reporting.

**Reactions associated with active comparator or placebo treatment**

The guideline indicates that serious unexpected ADRs, occurring in patients given active comparator agents as part of a clinical investigation, should be notified by the sponsor either directly to the appropriate regulatory authorities or to the product manufacturer. The sponsor is left to choose the recipient of the report.

The guideline also advises that events associated with administration of a placebo usually do not satisfy the criteria of a suspected ADR and, therefore, do not qualify for expedited reporting.

**Expedited notification of other safety information**

The E2A guideline indicates that there may be other situations that require rapid communication to relevant authorities, for example:

- an increase in the rate of occurrence of an ‘expected’ serious ADR that is judged to be clinically important;
- a significant hazard to the patient population, such as lack of therapeutic effect in patients with life-threatening conditions;
- a major safety finding from a newly completed preclinical study, such as a finding of positive carcinogenicity.

In these situations, the sponsor should apply medical and scientific judgement as to whether
the information materially influences the benefit–risk assessment of the study drug or whether it is sufficient to consider changes in the conduct of the clinical trial.

ICH E2B – Clinical safety data management: data elements for transmission of individual case safety reports

Background

A variety of regulations require individual case reports to be transmitted between various interested parties:

- from reporting sources to regulatory authorities and/or pharmaceutical companies;
- between regulatory authorities;
- between pharmaceutical companies and regulatory authorities;
- within regulatory authorities or pharmaceutical companies;
- from regulatory authorities to the WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden.

Although transmission of this information has generally been paper-based, in recent years there has been increasing use of electronic media for this purpose, whether through on-line access, tape or file transfer. Hence, it has become necessary to develop an electronic format capable of accommodating database-to-database transmission and taking advantage of the definition of common data elements and standard transmission procedures. These have given rise to the development of the E2B and M2 EWGs respectively.

The E2B EWG had the objective of standardizing the data elements needed for the transmission of ICSRs, regardless of source and destination. The scope of this topic did not encompass the definition of database structures, the design of paper report forms, QC/QA aspects or technical security issues.

The E2B guideline reached Step 4 in July 1997 and has since formed the basis of schemes for the electronic communication of safety data, for expedited and/or periodic reporting purposes within all ICH regions.

Data elements

In essence, ICH E2B defines data elements that could be useful in the clinical assessment of an individual case report. They are sufficiently comprehensive to cover complex reports from most sources, different data sets and transmission situations or requirements. Equally, the guideline acknowledges that there are many case reports that lack a substantial number of data elements, and as such they would not be available for inclusion in a transmission. Hence, the guideline serves to provide data elements that might cover each conceivable circumstance.

The guideline has also accounted for the fact that the same data can be provided in different ways, e.g. age information can be sent as the date of birth and date of reaction/event, age at time of reaction/event or patient age group according to the available
information. In this example, age would be provided by the most appropriate set of data elements rather than including multiple elements or redundant data.

Although structured data are recommended for transmission between databases, the E2B guideline makes provisions for the transmission of some free-text items, including a free-text narrative summary, as safety databases often contain large amounts of unstructured data.

**Minimum information**

The E2B guideline supports the criteria specified by ICH E2A with regard to the minimum information required for an ADR case report. In addition, it indicates that any one of several data elements is considered sufficient to define an identifiable patient (e.g. initials, age, gender) or reporter (e.g. initials, address, qualification) and that the patient and reporter may be the same individual and still fulfil the criteria for minimum information.

In addition, the following administrative information is required as a minimum for an electronic report:

- sender identification
- report identification number
- date of receipt of most recent information.

**Content of the data**

The E2B guideline divides the data elements into sections pertaining to administrative and identification information (Section A) or information on the case (Section B).

**Section A: administrative and identification information**  This section contains information necessary for identifying the report, reporter and different persons or institutions involved in the processing of the report, as well as indicators of specific report management, divided into three subsections:

A.1 Identification of the case safety report
A.2 Primary source(s) of information
A.3 Information on sender and receiver of case safety report

**Section B: information on the case**  This section allows for the collection and transmission of comprehensive information on the case, whether as structured information or as free text in many instances, divided into five subsections:

B.1 Patient characteristics
B.2 Reaction(s)/event(s)
B.3 Results of tests and procedures relevant to the investigation of the patient
B.4 Medicinal product(s) information
B.5 Narrative case summary and further information
Parent–child reports

Although such events are uncommon, the E2B guideline makes specific provision for case reports that relate to ADRs in the offspring of parents taking a suspect drug. When a report concerns an ADR in a child (or foetus), the details of the child or foetus should be regarded as the primary information for Section B, i.e. the patient characteristics should describe the child or foetus, whilst the mother (or father) should be described in the parent-specific subsection.

If the ADRs occur in both parent and child or foetus, then a separate case report should be completed for each, together with appropriate cross-references between the two.

The management of case reports that relate to spontaneous abortions or miscarriages is specifically addressed within the E2B guideline. Section B.4 of the E2B guideline indicates that case reports relating to foetuses should only be recorded as such if they concern identified foetal abnormalities or death. This section also states that early spontaneous abortion, an event that occurs in a significant proportion of pregnancies, should be treated as a parent reaction.

ICH E2C – Clinical safety data management: periodic safety update reports for marketed drugs

The E2C EWG was formed with the objective of creating a guideline on the format and content of PSURs relating to marketed products, rather than investigational compounds. The guideline reached Step 4 in November 1996 and has been formally implemented within the EU and Japan. Although E2C has not yet been formally adopted in the USA, the FDA has accepted PSURs produced in accordance with E2C standards, subject to a waiver against the regulated periodic reporting requirements. More recently, they have issued a proposed rule indicating that formal implementation of E2C will occur in due course.

An addendum to E2C has recently been developed, reaching Step 4 in February 2003. The addendum takes into account issues arising from interpretation of the original E2C guideline by regulatory authorities and relevant recommendations from the CIOMS V report.

The E2C guideline and its addendum endorse the fundamental principle established in the CIOMS II report that all relevant safety information should be presented, together with a critical clinical evaluation, covering data sets that span 6-month intervals. However, the guideline does not specify the schedule for submission of PSURs, leaving it to be determined by local regulatory requirements.

General principles incorporated within the guideline and its addendum include the following:

- A single PSUR should cover all dosage forms, formulations and indications for a given pharmacologically active substance; separate presentations may be used within that PSUR for different dosage forms, indications or patient populations.

- Information on a combination product may be presented in a separate PSUR, with cross-reference to the single agent(s) PSUR(s), or as a subsection within one of the single agent PSURs.
• Cumulative data are only required with respect to information presented on regulatory status and the summary of serious unlisted ADRs; all other data presented within the report should be derived only from the period covered by the report

• The schedule for submitting PSURs should be based on the date of first market authorization for the product, i.e. the IBD, regardless of the dosage form, formulation or uses covered by the report; manufacturers are encouraged to synchronize national birthdates (i.e. the date of national authorization) with the IBD in order to facilitate the production of a single PUR that can be submitted to multiple regulatory authorities on a simultaneous basis

• Subject to discussion with the relevant regulatory authorities, the ‘clock’ may be restarted (i.e. return to a 6 month submission schedule) after important additions or changes in clinical use are approved, e.g.:
  • a new, clinically dissimilar indication
  • a previously unapproved use in a special patient population, such as children, pregnant women or the elderly
  • a new formulation or new route of administration

• The ‘Company Core Data Sheet’ (CCDS) should form the basis for determining whether an ADR is ‘listed’ or ‘unlisted’; this should be used for inclusion of ADRs within the line listing, to determine whether clinically relevant changes have occurred to the safety profile of a product and whether there should be amendments to the relevant core prescribing text(s).

• The PSUR can refer to a lack of therapeutic effect in appropriate circumstances, e.g. with regard to medicinal products used in the treatment of life-threatening conditions.

**Content of the report**

Each PSUR should have 10 sections, namely:

1. Introduction
2. Worldwide market authorization status
3. Update of regulatory authority or market authorization holder (MAH) actions taken for safety reasons
4. Changes to reference safety information
5. Patient exposure
6. Presentation of individual case histories
7. Studies
8. Other information
9. Overall safety evaluation


**Regulatory information**

Each PSUR should be viewed as a ‘stand-alone’ document. Hence, the introduction to the report should place it in the context of previous reports and refer to associated products covered by separate reports (e.g. combination products).

Each PSUR should provide updates on the regulatory status of the product under review, including:

- a table indicating the worldwide marketing authorization status in all countries where a regulatory decision has been made about the product;
- an update of regulatory authority or MAH actions, with details on safety-related actions taken during the period under review and also since the data lock point.

For the 6-month and annual reports, the PSUR should use the version of the CCDS that was applicable at the start of the review period as the reference document and include it as an appendix to the report. If considered more practical, companies may use the CCDS that was in effect at the end of the reporting period for longer duration PSURs or Summary Bridging Reports. Whichever version of the CCDS is used as the reference document, this should be clearly stated within the text of the PSUR.

The report should indicate any changes made to the CCDS during the review period, together with a presentation of the modified sections. In addition, as there may be a delay between changing a CCDS and implementation of local label changes, the guideline recommends that each local operating company should provide a comment on any differences that exist between the CCDS and local safety information at the time of submitting the PSUR to their regulatory authority.

**Patient exposure**

The PSUR should provide an estimate of patient exposure covering the same period as the interval safety data. The report should describe the method used, such as:

- patient days
- number of prescriptions
- number of dosage units
- bulk sales (tonnage).

Whenever possible, the data should be provided by age and gender. If the PSUR includes data from clinical studies, then denominators from those clinical studies should also be provided.
Presentation of cases

The PSUR should incorporate data from all sources, including:

- direct reports to the company (spontaneous notifications, clinical studies, named-patient use);
- published literature;
- reports received from regulatory authorities;
- other sources, e.g. contractual partners, special registries, poison control centres or epidemiological databases.

Companies should use AE terms derived from their current terminologies in the line listings and summary tabulations. The usual practice is to include these at the preferred term level (or equivalent).

Line listings Specific ADRs should be presented as line listings that provide key information on individual case reports, thereby allowing regulatory authorities to select case reports for which they may require further detail when evaluating safety signals generated by the report. The line listings should be limited to the interval data relevant to the period under review. Selection of the ADRs is dependent upon the source of each case (see Table 9.2).

Table 9.2 ADRs that qualify for inclusion in a PSUR line listing

<table>
<thead>
<tr>
<th>Source of report</th>
<th>ADR type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous</td>
<td>Serious (all) and non-serious unlisted</td>
</tr>
<tr>
<td>Literature</td>
<td>Serious (all) and non-serious unlisted</td>
</tr>
<tr>
<td>Clinical trial or post-marketing surveillance (PMS) study</td>
<td>Serious</td>
</tr>
<tr>
<td>Named-patient or ‘compassionate’ use</td>
<td>Serious</td>
</tr>
<tr>
<td>Regulatory authority</td>
<td>Serious</td>
</tr>
</tbody>
</table>

Case reports should be organized by body system. Individual patients should only feature once within the line listing; those presenting with more than one ADR should be placed within the body system appropriate to the most clinically serious ADR.

Full details of content and format of the line listing are provided within the ICH E2C guideline.

Summary tabulations In addition to line listings, ICH E2C indicates that relevant safety information should also be presented as aggregate summary tabulations, organized by body system. This includes data from ‘other sources’ that may not have been presented in the line listings, e.g. non-serious listed spontaneous reports and serious ADRs from registries.
The E2C guideline provides a recommended format and indicates that there should be separate tabulations for:

- serious and non-serious ADRs
- listed and unlisted ADRs
- non-serious listed spontaneously reported reactions
- serious ADRs from ‘other sources’, sorted by source of information or country.

When there is a small number of cases, or the information is inadequate for any of the tabulations, a narrative description should suffice instead of a formal tabulation.

The data presented in the summary tabulations should be based on the interval data. However, a cumulative figure is required for serious unlisted ADRs, representing all cases reported to date, either in tabular form or as a narrative in the text of the report.

**Analysis of individual case histories** The company may present brief comments on individual case reports, for example a discussion on particular serious or unanticipated findings. However, the section allowing for these comments should not be confused with the global assessment in the Overall Safety Evaluation (see below).

**Studies**

The PSUR should contain information on the design and results of all relevant company-sponsored studies analysed during the period under review that contain important safety information, including relevant epidemiological, toxicological or laboratory investigations. In addition, the PSUR should contain a description of all new studies, initiated or being planned during the period under review, with respect to the evaluation of any safety issue.

Reports in the published literature that contain important safety information, including relevant abstracts from meetings, should be summarized and the publication references given.

**Other information**

Any unusual lack of therapeutic effect regarding a product used to treat serious or life-threatening diseases should be described, especially if it might represent a significant hazard to the treated patient population.

Any important safety information received after the data lock point should be presented in a separate section within the PSUR, including significant new cases or important follow-up data.

Information on specific risk management programmes for the product should also be discussed in this section. Likewise, when a comprehensive safety or benefit–risk analysis has been conducted, a summary of the analysis should be included in this section.
**Overall safety evaluation**

The overall safety evaluation should contain a concise analysis of the data presented within the PSUR, including important safety information received after data lock or resulting from the cumulative summary tabulations of serious unlisted ADRs. This section should include the company’s evaluation of the significance of the data and should highlight any new information on the following:

- change in the characteristics of listed reactions, e.g. severity, outcome, target population;
- serious unlisted reactions;
- non-serious unlisted reactions;
- increased frequency of listed reactions.

The information should be presented by System Organ Class (SOC) rather than by listedness or seriousness. Related terms, even if found in different SOCs, should be reviewed together for clinical relevance.

In addition, the evaluation should address any issues that have arisen with regard to the following (including lack of significant new information):

- drug interactions;
- experience with overdose (deliberate or accidental) and its treatment;
- drug abuse or misuse;
- positive or negative experiences during pregnancy or lactation;
- experience in special patient groups (e.g. children, elderly, organ-impaired individuals);

**Concluding statement**

The PSUR should conclude by indicating which safety data are not in accordance with the previous cumulative experience and/or with the current reference core prescribing text. It should then specify and justify any action that is recommended or has been initiated by the company.

**Summary Bridging Reports and Addendum Reports**

The addendum to E2C introduced two new concepts, Summary Bridging Reports and Addendum Reports, following on from recommendations from the CIOMS V report.

A Summary Bridging Report is a concise document integrating the information presented in two or more PSURs, to cover a specified period over which a single report is required by regulatory authorities, e.g. two consecutive 6-month reports for an annual report or 10 consecutive 6-month reports to make a 5-year report. The report should not contain any new
data but should provide a brief summary bridging two or more PSURs in order to facilitate assessment of the appended PSURs by the authority.

An Addendum Report is an update to the most recently completed PSUR and should be used when a regulatory authority requires a safety update outside the usual schedule based upon the IBD, e.g. in support of a local product licence renewal in Europe more than 6 months after the data lock point of the most recent 5-year PSUR. The report should summarize the data received between the data lock point of the most recent PSUR and the regulatory authority’s requested cut-off date. The report does not need to include an in-depth analysis of the additional cases, as these will be included in the next regularly scheduled PSUR.

Full details on the content and format of Summary Bridging Reports and Addendum Reports are provided in the CIOMS V report and the addendum to ICH E2C.

**ICH E6 – Good clinical practice**

Good clinical practice (GCP) is a standard for the design and conduct of clinical trials, providing assurance that the data and results are accurate and credible, and that the rights and confidentiality of trial subjects are protected. The E6 EWG issued a guideline for GCP that reached Step 4 in May 1996. The guideline has since been adopted in all three ICH regions, as well as other countries, e.g. Australia and Canada.

**Obligations of the investigator**

In addition to complying with applicable local regulatory requirements, the E6 guideline indicates that investigators should report all serious AEs immediately to the sponsor, except for those AEs that are exempted by the trial protocol or other trial documentation, e.g. the IB. In addition, AEs and/or laboratory abnormalities identified as critical to the safety evaluation should be reported to the sponsor in accordance with reporting requirements and time limits specified within the protocol. The investigator should also provide the sponsor and the IEC/IRB with any additional requested information on reported deaths, e.g. autopsy reports.

**Obligations of the sponsor**

The E6 guideline indicates that, in addition to complying with applicable regulatory requirements, the sponsor should notify promptly all concerned investigators, institutions and regulatory authorities of any finding that could adversely affect the safety of subjects participating in the clinical investigation or impact upon the conduct of the trial or alters the IRB/IEC’s approval/favourable opinion to continue the trial.

**Investigator’s Brochure**

The IB serves three functions:

- present clinical and non-clinical data relevant to the study of the investigational product in human subjects, thereby facilitating the investigators’ understanding of the benefit–risk of the proposed trial;
• detail specific safety monitoring procedures required during the course of the trial;

• serve as a reference document for sponsors when determining the ‘expectedness’ of an AE report for regulatory reporting purposes.

The ICH E6 guideline contains a recommended Table of Contents and suggestions for the content of each section of an IB. In particular, Section 6 of the IB should provide information on the safety experience in humans, including tabular summaries of ADRs from all clinical trials conducted to date and a discussion of any differences in pattern/incidence across indications or sub-groups. It should also provide a description of the possible risks and ADRs anticipated on the basis of prior experience with the investigational product and related products.

Section 6 should also present any significant information from marketed use in those countries where the product has been granted a marketing authorization, including relevant safety and efficacy information from the current core prescribing text(s) for that product.

**ICH M1 – Medical Terminology Expert Working Group**

Medical terminologies are required so that the verbatim terms used by reporters to describe AEs can be classified into a smaller number of clinically meaningful terms, whilst preserving some semblance of the original reporter’s intended description. This facilitates searches for related terms when evaluating specific safety issues as well as the preparation of line listings or summary tabulations for periodic reports.

Although various terminologies have been available for use for many years (e.g. COSTART, WHO-ART, ICD-9 and various company terminologies), many of the existing terminologies have been criticized for their lack of specificity, limited retrieval options and inability to handle complex combinations of signs and symptoms effectively. Hence, no medical terminology was accepted on a worldwide basis for regulatory reporting purposes.

In 1994, ICH formed the M1 Medical Terminology EWG as a multidisciplinary initiative with the objective of developing a single medical terminology that can be used for international regulatory purposes. They utilized the MEDDRA terminology, originally developed by the UK Medicines Control Agency (MCA), as its basis; eventually the new terminology became known as MedDRA (Medical Dictionary for Regulatory Activities). MedDRA was developed on the understanding that it should have relevance to all areas of drug and device regulation, i.e. not just for ADR reporting. Specific goals for its development included:

• ensure worldwide use through collaboration with and participation of stakeholders in its development;

• build from existing terminologies to maximize compatibility;

• provide mechanisms and structures that would facilitate translation into different languages;

• ensure long-term maintenance of the terminology beyond its initial implementation.
The ICH Steering Committee approved the M1 recommendations in July 1997. Thereafter, production versions were produced that included all COSTART, WHO-ART, J-ART, HARTS and relevant ICD-9-CM terms. This allowed all data previously coded using one of these terminologies to be capable of direct one-to-one matching with MedDRA terms (see Chapter 12 for further information).

Use of MedDRA for adverse drug reaction reporting

The FDA uses MedDRA in support of its AERS safety database. At present, it is not mandatory that a company pre-codes case reports in MedDRA before electronic notification to the FDA, whether for expedited reports or periodic safety updates.

Within the EU, MedDRA is used in support of the EudraVigilance database. With effect from January 2003, companies have been required to use MedDRA for pre-coding medical terms used when expedited reports are submitted electronically to the European Agency for the Evaluation of Medicinal Products (synonym: European Medicines Evaluation Agency; EMEA) and EU member state authorities. It is possible that the mandated use of MedDRA for other aspects of regulatory submission (e.g. clinical trial reports, periodic safety updates, marketing authorization application (MAA) submissions and product information) may follow in due course.

Within Japan, the MHLW issued guidance on the use of MedDRA in 1999, allowing companies to use MedDRA in support of ADR reporting, Japanese prescribing information texts, Japanese new drug application documentation and re-examination packages. In May 2002, the MHLW announced its plans for electronic ADR reporting, with initial implementation scheduled for October 2003 and becoming mandatory in due course, at which time the use of MedDRA in support of electronic ADR reporting will also become mandatory.

ICH M2 – Electronic standards for the transfer of regulatory information

The M2 EWG (Electronic standards for the transfer of regulatory information – ESTRI) was established in 1994 in order to define electronic standards that would facilitate electronic communication of clinical safety data between regulatory authorities, the pharmaceutical industry and other interested parties. The group planned to select standards from those already available in this field and recommend those that would have broad acceptance, be able to evolve with the development of technology, and that would be independent of the technical infrastructure used by a sender, receiver or vendor, thereby facilitating practical implementation in each ICH region.

The project includes the verification of procedures for consistent, accurate transfer of information, as well as the evaluation of encryption technologies and key certification procedures for the transfer of regulatory information.

Tests have been conducted to define logical electronic communication standards, to ensure the integrity of information and data exchange between companies and authorities. Tests have also involved the transfer of encrypted and non-encrypted files between a number of international centres.

As a result, the M2 EWG has made a series of recommendations relating to:

- implementation of electronic standards for the transfer of regulatory information and data (ESTRI)
• the Core Standard Set
• use of physical media (floppy disks and CD-ROM)
• network messaging
• secure electronic data interchange transmission over the Internet
• electronic document and message formats.

Guidelines issued by the project include ICH M2 E2B (M) (Electronic transmission of individual case safety reports message specification), which incorporates the ICH ICSR DTD version 2.1, in November 2000.

ICH E1 – The extent of population exposure to assess clinical safety

The E1 EWG was formed to develop a set of principles for the safety evaluation of drugs intended for long-term administration (more than 6 months) to patients with non-life-threatening diseases. The resultant guideline reached Step 4 in October 1994.

Key principles presented within the guideline include:

• Standards for the safety evaluation of drugs should be based on previous experience with the occurrence and detection of ADRs, and statistical and practical considerations.

• AEs are most frequent in the first few months of treatment; the number of exposed subjects should be large enough to observe whether the more frequent events (0.5–5 per cent) increase or decrease over time (300–600 patients should be adequate).

• Some patients should be treated for 12 months; 100 patients exposed for at least 1 year is considered acceptable.

• The total number of individuals treated, including short-term exposure, should be approximately 1500.

There are exceptions to these general standards, e.g. where there is:

• concern from clinical studies, other similar drugs or pharmacokinetic or pharmacodynamic properties of late onset ADRs;
• an expectation of low-frequency serious ADRs;
• only a small benefit from the drug;
• concern that the drug may add to a significant background morbidity or mortality.

The European Union

At present, the EU has 15 member state authorities, each setting regulatory requirements for ADR reporting from a framework of EC legislation and guidelines. Although there has been some attempt to harmonize regulatory requirements for the conduct of pharmacovigilance
within the EU, implementation of new legislation has not been a total success in this regard, as some authorities persist with divergent national practices.

**Legal basis and regulatory framework for adverse drug reaction reporting**


Although this legislation forms the basis for the present pharmacovigilance system in the EU, as shown in Table 9.3, it has necessitated a mixture of EU legislation, national legislation and various guidelines for full implementation. As a result of this regulatory framework, the decision to notify an ADR to the EU regulatory authorities has to take into account several factors in addition to its clinical characteristics:

- product status (investigational or marketed)
- source of the ADR (e.g. clinical trial or spontaneous report)
- country of origin (EU or non-EU)
- method of market authorization (centralized, mutual recognition or national procedure).

<table>
<thead>
<tr>
<th>Table 9.3</th>
<th>Regulatory framework governing expedited and periodic reporting requirements within the EU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigational products</td>
<td>Marketed products</td>
</tr>
<tr>
<td></td>
<td>• Council Directive 75/319/EEC (as amended)</td>
</tr>
<tr>
<td></td>
<td>• Commission Directive 2000/38/EC</td>
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<tr>
<td></td>
<td>Commission Regulation 540/95</td>
</tr>
<tr>
<td>Clinical Trial Directive guidelines</td>
<td>Pharmacovigilance Guidelinesa</td>
</tr>
<tr>
<td>CPMP guidelines ICH/135/95, ICH/287/95 and ICH/377/95</td>
<td>CPMP guidelines ICH/288/95, ICH/377/95, CPMP/175/95 and CPMP/183/97</td>
</tr>
<tr>
<td>National legislation</td>
<td>National legislation</td>
</tr>
</tbody>
</table>

a PhVWP/108/99 (December 2001).


The ‘Clinical Trials’ Directive was formally adopted and published as EU legislation on 4 April 2001, the objective being to provide uniform standards for the conduct of clinical trials across the EU, primarily in the interest of protecting subjects that take part in those clinical trials. Member states had until 1 May 2003 to apply the provisions of this directive through national legislation, although this has taken longer in most instances. National legislation should come into effect no later than 1 May 2004.
The Clinical Trials Directive applies to all clinical trials conducted within the EU, throughout all phases of clinical development (including bioequivalence and bioavailability studies), but does not apply to non-interventional trials. It stipulates that all clinical trials should be conducted and reported in accordance with the principles of GCP.

The ADR reporting requirements specified within the directive are generally in accordance with standards expressed within the relevant ICH guidelines, although the directive does contain provisions for annual safety reports, a relatively novel concept at the EU level for investigational products.

A series of guidelines were issued during April 2003 under the sponsorship of the EC in support of the Clinical Trials Directive. These include two guidelines related to clinical drug safety: Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use (‘ADR reporting’ guideline) and Detailed guidance on the European database of suspected unexpected serious adverse reactions (Eudravigilance – Clinical Trial Module) (‘SUSAR database’ guideline).


In 1993, the EC published legislation comprising Council Regulation (EEC) 2309/93 and Council Directive 75/319/EEC (as amended by Council Directive 93/39/EEC), which came into effect from 1 January 1995. Although the primary purpose of this legislation was to define the requirements for the approval and maintenance of MAAs, they also define the requirements for the conduct of pharmacovigilance by any company marketing medicinal products within the EU.

In addition to ‘ethical’ pharmaceutical products, the legislation applies to generic products available on prescription, over-the-counter products or those sold under licences for parallel imports. The regulation applies to all medicinal products registered under the ‘centralized’ process, including biotechnology products, and was immediately binding to all member states. The directive applied to all products registered under mutual recognition or national procedures, but it required endorsement through national legislation.

Commission Regulation 540/95 was implemented on 14 March 1995, as a supplement to Regulation 2309/93, specifically to clarify that pharmaceutical companies should notify all non-serious unexpected ADRs, for products authorized under the centralized procedure, in a separate section of PSURs, regardless of their country of origin.


Almost all member state authorities have issued legislation in accordance with Council Directive 93/39/EEC. However, there has been some variation in their interpretation of ADR reporting requirements, such that ADR reports still require consideration on a country-by-country basis when reporting to member state authorities.

Recently, as part of a mandatory review of existing pharmaceutical legislation, the EC has made proposals to amend many aspects of the EU medicines regulatory regime, as set out in Regulation 2309/93 and Directive 2001/83. The proposals include the following relevant to the conduct of pharmacovigilance:
replacement of 5-yearly product licence renewals with a system based on the submission of 3-yearly PSURs;

an enhanced role for the EC in the coordination of EU-wide pharmacovigilance and inspection work.

Committee for Proprietary Medicinal Products guidelines

The Committee for Proprietary Medicinal Products (CPMP) has provided several guidelines relating to expedited and periodic reporting for investigational and marketed products:

- ICH/135/95: Good clinical practice (implementing ICH E6)
- ICH/287/95: Data elements for transmission of individual case safety reports (ICH E2B)
- ICH/288/95: Periodic safety update reports for marketed drugs (ICH E2C)
- ICH/377/95: Definitions and standards for expedited reporting (ICH E2A)
- CPMP/175/95: Note for guidance on the procedure for competent authorities undertaking of pharmacovigilance
- CPMP/183/97: Conduct of pharmacovigilance for centrally authorized products.

Although these guidelines lack formal legislative power, it is generally accepted that they represent the requirements of member state authorities with regard to meeting reporting requirements. Hence, companies are advised to observe these guidelines, and the provisions of the Notice to Marketing Authorisation Holders (see below), when developing ADR reporting procedures.

Pharmacovigilance Guidelines

In accordance with Article 24 of Council Regulation 2309/93 and Article 29g of Council Directive 75/319/EEC (as amended), the CPMP drafted several guidelines in order to provide MAHs with guidance on the implementation and practical procedures involved in complying with the legislation. These were originally incorporated into Chapter V of the Notice to Marketing Authorisation Holders (synonym: Notice to Applicants), effective from 1 January 1995. This was superseded by formal incorporation of the guidance into Volume 9 of ‘The rules governing medicinal products in the European Union – Pharmacovigilance’ (synonym: Pharmacovigilance Guidelines) in December 2001.

Volume 9 is presented in four parts:

- Part I – pharmacovigilance of medicinal products for human use
- Part II – pharmacovigilance of medicinal products for veterinary use
- Part III – general information on EU electronic exchange of pharmacovigilance data
Part IV – general reference to administrative and legislative information relevant to human and veterinary products.

Perhaps of greatest practical relevance to meeting EU pharmacovigilance requirements, Part I contains the following chapters:

1. Notice to Marketing Authorisation Holders
   1.1 Legal basis and purpose
   1.2 Adverse reaction reporting
   1.3 Reporting requirements in special situations
   1.4 Periodic safety update reports
   1.5 Company-sponsored post-authorization studies
   1.6 Ongoing pharmacovigilance evaluation during post-authorization period

2. Guidance and procedures for competent authorities

3. Terminology

Upon issue, the foreword in Volume 9 indicated that certain chapters within Part I were expected to be revised during 2002 and legal references taking into account the ‘codified’ Council Directive 2001/83/EC, although this has yet to occur.

Data privacy legislation

Many EU member states have had legislation in place for several years to govern the privacy of personal data, reinforced by the issue of the Data Protection Directive (Council Directive 95/46/EEC) in October 1995 and its subsequent implementation though national legislation. The legislation has had a variable impact with regard to the management of drug safety information. In general, it should not prevent healthcare professionals from notifying ADRs to pharmaceutical companies, provided that appropriate informed consent is obtained from the patient and anonymity preserved to the extent required by local laws.

However, company pharmacovigilance departments need to be aware of the legislation so that they do not contravene national laws when managing ADR data, especially when communicating to third parties in non-EU countries. In particular, companies need to take into account the provision that personal data should not be communicated to ‘third’ countries that do not maintain comparable standards of privacy protection. In such circumstances, possible solutions to this issue may need to be considered:

- utilize an exemption, provided by the directive, that allows for the transfer of data to a ‘third’ country for reasons of substantive public interest;

- develop inter-affiliate contracts to ensure that data transferred from the EU are handled in accordance with European law;
• anonymize the data in accordance with EU data privacy legislation before transfer to a ‘third’ country.

**Role of member state authorities**

Council Regulation 2309/93 and Council Directive 2001/83/EC require that each member state should establish a pharmacovigilance system for the collection and evaluation of safety information relating to marketed medicinal products, and take appropriate measures to encourage doctors and other healthcare professionals to report suspected ADRs to member state authorities. Details of the requirements are specified within CPMP guideline CPMP/175/95 (revised 1998). These cover the following topics:

- Establishment of a pharmacovigilance system
- Management of pharmacovigilance data
  - spontaneous reporting systems
  - company-derived pharmacovigilance data
  - pharmacovigilance data from other sources
  - procedures for communication and evaluation of pharmacovigilance issues within the EU, including:
    - transmission of ADR reports (to MAHs)
    - transmission and management of detected signals
    - evaluation of company-sponsored post-authorization safety studies
    - evaluation of PSURs
    - special safety monitoring of medicinal products
    - electronic data transmission.

Specifically, the guideline instructs member state authorities to:

- Notify all serious ADRs occurring within their respective countries to the relevant MAHs, and the EMEA, within 15 days of receipt of information from local healthcare professionals; the data should be sufficient to allow an evaluation of each ADR, although it is not mandatory for the authority to have made a formal evaluation before notification to the MAH.

- Make information on non-serious ADR reports available in summary form to all relevant parties, including MAHs.

- Regarding ADR reports received from MAHs, each authority should ensure that:
  - reports submitted by an MAH conform to Pharmacovigilance Guidelines, and that
all data included in these reports are validated and verified, as far as possible, and that these reports are followed up by the MAH, where appropriate;

- PSURs are evaluated and, if a Reference Member State, assessment reports are issued;
- the progress of post-authorization safety studies should be reviewed on a regular basis; final study reports should be evaluated and changes to the Summary of Product Characteristics (SPC) made, if appropriate.

- Ensure that they have the capability to send and receive ADR reports electronically.

**European Agency for the Evaluation of Medicinal Products**  Council Regulation 2309/93 also established the EMEA, situated in London. Initially, the EMEA's primary role related to medicinal products authorized under the ‘centralized’ procedure. Recently, their role has seemingly broadened and will soon encompass investigational products as well as marketed products subject to mutual recognition procedures or national authorization procedures.

**EudraVigilance**  EudraVigilance is the EU’s new data-processing network and database management system, financed by the EC, for the exchange, processing and evaluation of safety data relating to marketed products, and came into operation on 5 December 2001. Further development in the system’s functionality is expected to occur during 2003 and 2004, including provision for a Clinical Trial Module.

EudraVigilance has been presented as a milestone in the development of electronic exchange of pharmacovigilance data, between member state authorities and also between companies and authorities. Its main functional components are:

- EudraVigilance Gateway for the secure transmission of ICSRs;
- EudraVigilance Database Management System, including the safety and acknowledge-ment message exchange, routing and loading mechanisms, the guided ICSR creation procedure, the user management and security mechanisms;
- EudraVigilance Standard Terminology, with a focus on MedDRA and a product dictionary being developed by the EMEA.

**Definitions**

Although the EU legislation incorporates most of the relevant ICH definitions, there are some anomalies. However, most have minimal impact upon company working practices and are not considered further.

Guidelines supporting the Clinical Trials Directive have introduced the concept of suspected unexpected serious adverse reactions (SUSARs), with regard to expedited reporting requirements, seemingly without definition. However, it is evident that these simply refer to ADRs that are serious and unexpected in nature.


*Health professional*

At present, companies are required to notify only those cases that have been confirmed by health professionals to EU authorities, whether for investigational or marketed products. These are defined within the Pharmacovigilance Guidelines as medically qualified doctors, dentists, pharmacists, nurses and coroners.

When a report originates from a pharmacist or nurse, the company should attempt to obtain further information about the case from a medically qualified doctor responsible for the patient.

*General requirements*

The Pharmacovigilance Guidelines indicate that the MAH must ensure that it has an appropriate system of pharmacovigilance in place within the company in order to assure responsibility and liability for its products on the market and to ensure that appropriate action can be taken.

In addition, since 1995, any company marketing a medicinal product within the EU should have ‘permanently and continuously at its disposal’ within the European Economic Area (EEA; i.e. EU plus Iceland, Liechtenstein and Norway) a ‘qualified person’ responsible for pharmacovigilance at the EU level. This person should have experience in all aspects of pharmacovigilance and, if not medically qualified, should report to or have access to a medically qualified person. Otherwise, the qualifications necessary for filling such a role are less well defined than those evident for the person with analogous responsibilities for manufacturing standards.

The MAH should provide the name of the qualified person to all member state authorities and, for centrally authorized products, to the EMEA.

Although it is clear that each company must have at least one qualified person resident within the EEA, the Pharmacovigilance Guidelines recognize that national regulations in some member states require a nominated individual from within that country who has specific legal obligations with regard to the conduct of pharmacovigilance at a national level (e.g. France, Germany and Spain).

The responsibilities of the qualified person are:

- Establish and maintain a system that ensures that information about all suspected ADRs reported to company staff, including medical representatives, is collected and collated so that it may be accessed at a single point within the EU.

- Prepare expedited ADR reports, PSURs and company sponsored post-authorization study reports for the EMEA and member state authorities in accordance with the respective requirements of Council Regulation 2309/93 and Council Directive 2001/83/EC.

- On-going pharmacovigilance during the post-authorization period, ensuring that any request from member state authorities, for the provision of additional information necessary for the evaluation of benefits and risks of a medicinal product, is answered fully and promptly, including provision of sales/prescription information for the product concerned.
- Provision to member state authorities of any other information relevant to the evaluation of benefits and risks of a medicinal product, including appropriate information on post-authorization safety studies.

**Licensing agreements**

The Pharmacovigilance Guidelines contain specific requirements relating to licensing agreements between pharmaceutical companies. Part I Section 1.1.1 requires MAHs to ensure that the arrangements for meeting pharmacovigilance obligations are specified in writing to relevant member state authorities at the time that an authorization is granted, and subsequently when any changes to the arrangements are proposed.

In addition, Part I Section 1.2.2 indicates that the ‘clock’ for expedited reporting starts as soon as any personnel of the MAH receive the minimum information. However, wherever possible, the time frame for regulatory submission should be no longer than 15 days from first receipt by the second company, and explicit procedures and detailed agreements should exist between the MAH and the second company to facilitate achievement of this objective. Although challenging, these requirements seemingly take into account the consideration that the MAH cannot have sufficient control over, or be made responsible for, the operations of the partner company and that each ADR report usually has to be processed at least twice before notification to regulatory authorities.

**Review of scientific literature**

The Pharmacovigilance Guidelines indicate that the MAH is expected to ‘screen the relevant worldwide scientific literature’ and report suspected ADRs arising from this source in accordance with expedited and periodic reporting provisions. Although the guidance is ambiguous, in that it fails to define the terms ‘screen’ or ‘relevant’, it is generally accepted that companies should review relevant journals from across the world, with relevance being determined by the nature of the medicinal product sold within the EU. The review should have two objectives:

- to discover suspected ADRs relating to identifiable patients;
- to identify new safety issues that might impact on the benefit–risk of the marketed product.

The Pharmacovigilance Guidelines (Part I Section 1.2.2) indicate that the regulatory ‘clock’ should start on the date that the MAH first becomes aware of the article or case report. This takes into account the consideration that there is often a time lag between the date of publication of an article and access by the MAH, as determined by the arrival of the relevant journal on site, its availability on MedLine or other recognized literature databases, or its international broadcast in publications that summarize the literature.
Reporting requirements for investigational products

**Expedited reports**

The Clinical Trials Directive stipulates that clinical investigators should notify serious AEs, and other safety-related information to the sponsors of clinical trials to standards that are in accordance with the ICH E6 guideline. Once notified to the sponsor, each serious AE should be assessed opposite national expedited reporting requirements and notified accordingly.

Although CPMP guideline ICH/377/95 endorsed the ICH E2A guideline, it was formally implemented in only a small number of member states. Hence, at present, expedited reporting requirements vary across member states to a considerable extent, as illustrated in Table 9.4. This situation should change with implementation of the Clinical Trials Directive, which will require that member states implement 7 and 15 day requirements in full accordance with ICH E2A.

<table>
<thead>
<tr>
<th>Country</th>
<th>ADR type</th>
<th>Local origin</th>
<th>Foreign origin</th>
<th>Time frame (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>Serious</td>
<td></td>
<td>Not required&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Not specified</td>
</tr>
<tr>
<td>Belgium</td>
<td>Serious&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Serious&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td>Not specified</td>
</tr>
<tr>
<td>Denmark</td>
<td>Serious&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Serious unexpected&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>Not specified</td>
</tr>
<tr>
<td>Finland</td>
<td>Serious unexpected</td>
<td>Not required&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>7/15</td>
</tr>
<tr>
<td>France</td>
<td>Serious&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Serious unexpected&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td>7/15</td>
</tr>
<tr>
<td>Germany</td>
<td>Serious</td>
<td></td>
<td>Serious</td>
<td>15</td>
</tr>
<tr>
<td>Greece</td>
<td>Serious</td>
<td></td>
<td>Serious unexpected&lt;sup&gt;f&lt;/sup&gt;</td>
<td>15</td>
</tr>
<tr>
<td>Ireland</td>
<td>Serious</td>
<td></td>
<td>Serious unexpected</td>
<td>15</td>
</tr>
<tr>
<td>Italy</td>
<td>Serious unexpected</td>
<td></td>
<td>Serious unexpected</td>
<td>7/15</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>Serious</td>
<td></td>
<td>Not required</td>
<td>Not specified</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Serious unexpected</td>
<td></td>
<td>Serious unexpected</td>
<td>7/15</td>
</tr>
<tr>
<td>Portugal</td>
<td>Serious</td>
<td></td>
<td>Serious unexpected&lt;sup&gt;g&lt;/sup&gt;</td>
<td>15</td>
</tr>
<tr>
<td>Spain</td>
<td>Serious unexpected</td>
<td></td>
<td>Serious unexpected</td>
<td>7/15</td>
</tr>
<tr>
<td>Sweden</td>
<td>Serious unexpected</td>
<td></td>
<td>Serious unexpected</td>
<td>7/15</td>
</tr>
<tr>
<td>UK</td>
<td>Serious unexpected</td>
<td></td>
<td>Serious unexpected</td>
<td>7/15</td>
</tr>
</tbody>
</table>

<sup>a</sup> Report only if having an impact upon the conduct of clinical trials in that country.
<sup>b</sup> Only once MAA submission has been made.
<sup>c</sup> To be reported by investigators; report events rather than reactions.
<sup>d</sup> If drug- or trial-related.
<sup>e</sup> All serious if from a multicentre trial involving French centres (drug- or trial-related).
<sup>f</sup> Only if from non-EU countries.
<sup>g</sup> If from a multicentre trial involving Portuguese centres.

The ‘ADR reporting’ guideline clarifies that expedited reporting requirements will apply to all SUSARs associated with the investigational product regardless of which trial they occur in, whether within the EU or a third country, as well as those that arise from other sources such as spontaneous reports, the published literature or those transmitted to the sponsor by another regulatory authority.

Once implemented, the Clinical Trials Directive will require sponsors to provide the same information to ethics committees as and when notified to ‘concerned’ member state
authorities. In addition, sponsors are to keep all ‘concerned’ investigators informed. The ‘ADR reporting’ guideline provides clarification with regard to both of these requirements.

Sponsors should notify SUSARs to all ethics committees that have approved clinical trials on the related investigational product simultaneous with notification to the authorities. Notification should generally be via the issue of individual case reports to the ethics committees, although sponsors may use a periodic line listing (accompanied by a summary report) for notification to an ethics committee of SUSARs from outside of the ethics committee’s home country, if they wish.

Notification to an ethics committee may also be delegated from the sponsor to the coordinating/principal investigator in some circumstances.

The sponsor should immediately inform all investigators with regard to findings that could adversely affect the safety of subjects participating in ongoing or planned clinical trials. Safety issues that impact upon the course of a clinical trial or development project should also be considered significant; these include suspension of the trial programme and safety-related amendments to trial protocols.

Otherwise, safety information may be provided to investigators as an aggregated line listing of SUSARs on a periodic basis, the periodicity being determined by the nature of the clinical development project and the volume of SUSARs generated. The line listing should be accompanied by a concise summary of the evolving safety profile of the investigational product. With regard to data from blinded clinical trials, the line listing should present data on all SUSARs, regardless of the medication administered, with the blind maintained.

In addition, the ‘ADR reporting’ guideline indicates the following:

- All case reports will require causality assessments; this requirement will apply equally to serious and non-serious AEs reported during the conduct of clinical trials; in addition, reports submitted to the authorities should include both the investigator and sponsor causality assessments when these differ.

- Treatment codes should always be broken before serious unexpected ADRs are reported to the competent authorities and ethics committees:
  - cases involving placebo do not meet the criteria for expedited reporting;
  - the ‘blind’ should be maintained for those persons responsible for the analysis and interpretation of results.

- Expedited reports will also be required for any finding that could affect ongoing benefit–risk assessment of the investigational product or would be sufficient to require changes to the conduct of a clinical investigation; this includes serious ‘protocol-related’ events.

- Annex 3 of the guideline presents details on the data elements for inclusion in expedited reports; reports should include the relevant ‘Eudract’ number plus the sponsor’s case report reference number; reports with insufficient information may be returned to the company for completion and resubmission.

- In due course, electronic reporting will be the expected method for the notification of
SUSARs to the authorities, using the format and content as defined within the ‘SUSAR database’ guideline; until then, the CIOMS-I form will be accepted, although other important observations qualifying for expedited reporting should be notified by letter.

**Periodic reports**

At present, only a few EU member states have periodic reporting requirements for investigational products (see Table 9.5). Again, this situation will change with implementation of the Clinical Trials Directive, which requires that the sponsor should provide information to relevant member state authorities and ethics committees relating to the safety of subjects participating in clinical trials in the EU. Although the Clinical Trials Directive indicates that periodic reports should be submitted annually on a trial-by-trial basis, the ‘ADR reporting’ guideline indicates that companies will be allowed to prepare a single periodic report to cover each clinical development programme, to an annual schedule determined by the date of first authorization of a clinical trial by a member state authority.

<table>
<thead>
<tr>
<th>Country</th>
<th>Periodic reporting requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>Not required</td>
</tr>
<tr>
<td>Belgium</td>
<td>Not required</td>
</tr>
<tr>
<td>Denmark</td>
<td>Not required</td>
</tr>
<tr>
<td>Finland</td>
<td>Annual report (list of serious ADRs and summary of safety)</td>
</tr>
<tr>
<td>France</td>
<td>Not required</td>
</tr>
<tr>
<td>Germany</td>
<td>Not required</td>
</tr>
<tr>
<td>Greece</td>
<td>Not required</td>
</tr>
<tr>
<td>Ireland</td>
<td>Line-listing (non-serious ADRs) at end of study</td>
</tr>
<tr>
<td>Italy</td>
<td>Semi-annual reports (serious ADRs and summary of ongoing/completed studies)</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>Not required</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Not required</td>
</tr>
<tr>
<td>Portugal</td>
<td>ADRs to be listed in copy of study report</td>
</tr>
<tr>
<td>Spain</td>
<td>Annual report (list of serious ADRs and summary of safety)</td>
</tr>
<tr>
<td>Sweden</td>
<td>Annual reports, provided by investigators and sponsors (serious ADRs, withdrawals due to ADRs, progress of trial)</td>
</tr>
<tr>
<td>UK</td>
<td>Reports on completion of individual studies and at time of update/renewal of CTX (summary tabulations and comments)</td>
</tr>
</tbody>
</table>

Each report should include:

- A line listing of all serious ADRs that have occurred during the period under review; these should be presented trial by trial.
- Aggregate summary tabulations of serious ADR terms; to be presented trial by trial.
- A summary overview of the subjects’ safety, to include:
  - a concise benefit–risk evaluation of the product under study;
– supporting results of non-clinical studies or other experience with the investigational product that are likely to affect the subjects’ safety;

– where appropriate, measures proposed to minimize identified risks, including a detailed rationale with regard to any proposals to amend trial protocols, to change or update the consent form, patient information leaflet and/or the investigator’s brochure.

Annexes 4 and 5 of the ‘ADR reporting’ guideline provide further detail on the content of the line listings and summary tabulations respectively.

**Reporting requirements for marketed products**

Although expedited and periodic reporting requirements for marketed products are defined in Council Regulation 2309/93 and Council Directive 2001/83/EC, a single standard currently does not exist within the EU, due to the impact of national legislation. However, there are elements common to all member states, as presented by the guidance contained within the Pharmacovigilance Guidelines.

**Expedited reports**

MAHs should submit expedited reports to relevant member state authorities (including the EMEA) within 15 calendar days following receipt of relevant information. In principle, ADR reports should be notified as follows:

- ADRs originating from within the EU – report all serious ADRs to the member state authority where the reaction occurred and, if subject to mutual recognition or referral, also to the reference member state;

- ADRs originating outside the EU – report serious unexpected ADRs to all member state authorities (where authorized) and the EMEA.

In practice, the above requirements hold true across all member states for products authorized under the centralized requirements. However, requirements for products subject to mutual recognition or national authorization procedures vary across some member states (see Table 9.6).

The Pharmacovigilance Guidelines indicate that reporting forms acceptable to member state authorities should be used until electronic reporting standards are established and implemented (see below). Paper-based forms may be computer generated but should follow an accepted content and layout.

The Pharmacovigilance Guidelines indicates that reports from post-authorization studies should be unblinded by the sponsor prior to reporting. However, cases of serious expected ADRs should only be reported in an expedited manner if the blind has already been broken for some other reason. Otherwise, reporting may be deferred until the study has been completed and the study data locked. The Pharmacovigilance Guidelines also confirm that reports from post-authorization studies that qualify as clinical trials will be subject to the requirements of the Clinical Trials Directive from its date of implementation.
Evaluation of case reports  The EU legislation does not mandate causality assessments on individual ADR case reports for marketed products. However, the Pharmacovigilance Guidelines indicate that MAHs may opt to comment whether they consider that there is a causal association between the reported suspect product(s) and reaction(s), together with the criteria used for the assessment. However, some member states retain local requirements for mandatory assessments, e.g. France (‘imputability’) and Germany (‘scientific evaluations’).

The CPMP Pharmacovigilance Working Party has recommended that regulatory authorities and companies perform causality assessments using an ‘ABO’ classification, as presented below:

A  ‘Probable’ – the case report contains a good rationale and sufficient documentation to support a causal relationship in the sense of it being plausible, conceivable or likely (but not necessarily highly probable).

B  ‘Possible’ – the case report contains sufficient information to consider a causal relationship as possible, in the sense of it being not impossible and not unlikely, although the relationship may be uncertain or doubtful; for example, because of missing data or insufficient evidence.

O  ‘Unclassified’ – the causality of the case report cannot be assessed for one or more reasons; e.g. insufficient evidence, conflicting data or poor documentation.

In addition, the Pharmacovigilance Guidelines indicate that, ‘in exceptional cases, when a
reported ADR impacts significantly on the established safety profile of the product’, the MAH should indicate this within the report. Examples include:

- the report is one of a series of similar or linked cases;
- there is *prima facie* evidence in favour of a causal relationship for a serious unexpected ADR;
- there is a suggested change in the nature, severity or frequency of expected ADRs;
- new risk factors are identified.

Information on the frequency of ADRs should provide the basis on which the estimate has been made, including data on the total number of ADR reports and patient exposure.

**Special situations**  The Pharmacovigilance Guidelines specify reporting requirements for several ‘special’ situations:

1. Reporting during the period between MAA submission and approval.
   ADR reporting should be in accordance with clinical trial regulations. In addition, the applicant should expedite reporting of any information that impacts upon the ongoing benefit–risk assessment, e.g.:
   - a serious unexpected ADR that has good evidence of a causal relationship;
   - multiple reports of serious unexpected ADRs where there is a possible relationship;
   - suspicion of change in frequency or severity of a known effect;
   - results from studies which impact on efficacy assessment.

2. Reporting of outcomes of use during pregnancy.
   MAHs are expected to follow up all reports of pregnancy. Abnormal outcomes are subject to post-marketing expedited and periodic reporting requirements. In addition, reports from prospective registries should be evaluated and information included in PSURs, including:
   - details of cases during report period;
   - aggregated data of overall exposure and normal/abnormal outcomes.

3. Reporting from other post-marketing initiatives.
   This section distinguishes between situations where there is a systematic process for reporting of adverse events and where no such process exists. The MAH should report only those events that are specifically reported as serious ADRs, as for expedited reports from post-authorization studies.

4. Compassionate use/named patient supplies.
   The MAH should establish a protocol for controlling the supply of a medicinal product for compassionate/named-patient use, which encourages the prescriber to report any
suspected ADRs to the company (and competent authority if required on a national basis).

5. Lack of efficacy.
Reports of lack of efficacy are not normally subject to expedited reporting within the EU but should be discussed in the relevant PSUR(s). However, expedited reports may be required if lack of efficacy occurs in certain circumstances, e.g. treatment of life-threatening disease, vaccines and contraceptives, or where lack of efficacy indicates a change in the benefit–risk balance, e.g. lower than expected efficacy or higher than expected death rate due to progressive disease in the case of anti-neoplastic agents.

6. Reporting of overdoses and abuse.
The MAH should report cases of overdose and abuse (accidental or intentional) that lead to serious (EU) or serious unexpected (non-EU) ADRs. This includes reports that indicate that the taking of the product led to suicidal intention and a subsequent overdose of the same or different medicinal product. However, it does not include reports of overdose or abuse that have no associated ADR, although follow-up is required to obtain relevant details.

7. Reporting of misuse.
The MAH should collect any available information related to misuse of its products, which may have an impact on their benefit–risk evaluations, and provide expedited reports for any cases of misuse that lead to serious (EU) or serious unexpected (non-EU) ADRs.

Periodic safety update reports
Companies operating within the EU are required to submit PSURs to member state authorities and the EMEA (for products authorized under the centralized procedure) in accordance with Council Regulation 2309/93 and Council Directive 2001/83/EC. Full details of the requirements are provided within the Pharmacovigilance Guidelines, which indicate that the content and format of the PSURs should generally be in accordance with standards expressed in the ICH E2C guideline.

Schedule for submission  PSURs should be prepared at the following intervals, unless specified otherwise as a condition of marketing authorization:

- six-monthly for the first 2 years after authorization;
- annually for the subsequent 3 years;
- at the time of first licence renewal;
- thereafter five-yearly (at the time of licence renewal).

The MAH’s safety database should be frozen at the time points defined above (‘data lock points’). Each report should cover the period since the last PSUR and be issued within 60 calendar days of the data lock point.
The Pharmacovigilance Guidelines indicate that the schedule for submission may be reset to ‘zero’ when a product receives approval for a new indication, dosage form, route of administration or patient population beyond the initial authorization for the active substance. Unfortunately, member state authorities have been inconsistent in their interpretation of this requirement, leading to some practical difficulties for MAHs.

**Birth dates** The EU legislation specifies a periodicity for PSURs based upon the date of marketing authorization within the EU. Therefore, although the principle of an IBD was supported by the EC through their endorsement of the ICH E2C guideline, each product should have an EU birth date based upon procedure used for marketing authorization:

- centralized procedure – date of marketing authorization granted by the EC;
- mutual recognition – date of marketing authorization granted by the reference member state;
- national – the MAH may propose an EU birth date that can be applied to reporting requirements across member states.

In order to harmonize the international production of PSURs, the Pharmacovigilance Guidelines have allowed some flexibility in this requirement, to the extent that the IBD can be used to determine the schedule for submission of PSURs within the EU provided that the IBD is within 6 months of the EU birth date. Nevertheless, some national authorities have persisted with a requirement for submission of PSURs based upon the national approval dates. In practice, companies may circumvent this requirement by submitting selected PSURs early in order to synchronize the schedule across member states.

One further difficulty has arisen when some member state authorities have required updates to 5-year PSURs submitted in support of product licence renewals, if the time of renewal is in excess of 6 months from the time that the previous 5-year PSUR was written. Companies have been able to overcome this obstacle in many instances by submitting line listings and short summaries of regulatory actions and safety issues that cover the intervening period.

**Content of reports** Member state authorities require and/or accept PSURs produced in accordance with the content and format specified within the ICH E2C guideline, as subsequently supported by guidance provided within the Pharmacovigilance Guidelines.

In addition, for products authorized under the centralized procedure, in accordance with Commission Regulation 540/95, all non-serious unexpected ADRs should be included within the relevant PSUR, regardless of their source or country of origin, usually as a separate line listing. These ADRs should also be considered as part of the overall evaluation of the ongoing safety profile of the product under review.

**Variations in Summary of Product Characteristics** The Pharmacovigilance Guidelines requires that, if the PSUR indicates that the new safety information warrants an amendment to the SPC, the variation application should be submitted at the same time as the PSUR. Two factors sometimes make it difficult for companies to comply with this requirement:
• in-house processes often require lengthy consideration of proposed label changes, taking the decision point beyond 60 days from the data lock point;

• review of the data presented in the PSUR may generate new safety signals that will then require detailed evaluation, something that may take more than the 60 days allowed from the data lock point if the evaluation is to be thorough and considered.

**Inconsistencies in EU requirements for periodic safety update reports**  Since implementation of the current EU requirements for PSURs, it has become evident that several member states persist with specific national requirements in addition to the general requirements detailed above. These include:

• France, Germany, Portugal, Spain – national birth dates are applied, although they do allow companies to synchronize these with the EU birth date.

• France and Germany appear to have a relatively low threshold for resetting clock start.

• Italy requires PSURs per EU schedule *plus* abridged semi-annual reports.

• Germany requires PSURs per EU schedule *plus* 2-year and 5-year ‘experience’ reports.

• UK, Germany, Greece – line-listings to include non-serious listed ADRs (usually as an addendum to the report).

• Ireland – MAH to provide non-serious listed ADRs upon request.

• Belgium – PSUR to include scientific evaluation and benefit/risk statement in Dutch or French.

• Belgium, Denmark, Finland, Germany, Italy and Sweden often require *ad hoc* reports in support of product licence renewals.

**Post-authorization safety studies**

Post-authorization safety studies (PASSs) may be conducted for a variety of reasons:

• to identify previously unrecognized safety issues;

• to investigate possible safety hazards;

• to confirm the safety profile of a product under marketed conditions;

• to quantify or identify risk factors for established ADRs;

• to explore the clinical relevance of toxic effects apparent in pre-clinical studies.

Although the Notice to Applicants has specified requirements for the conduct of PASSs for a number of years, the legal basis for these provisions was provided by Commission Directive 2000/38/EC. The directive defines a PASS as ‘a pharmaco-epidemiological study or a
clinical trial carried out in accordance with the terms of the marketing authorization, conducted with the aim of identifying or quantifying a safety hazard relating to an authorized medicinal product’. This definition seemingly limits PASSs to:

- observational post-marketing surveillance or pharmacoepidemiological studies;
- ‘Phase IV’ clinical trials (i.e. clinical trials within the terms of the approved SPC), with evaluation of clinical safety as a primary objective.

However, the Pharmacovigilance Guidelines complicate matters by indicating that, in addition to the above definition, ‘any study where the number of patients to be included will add significantly to the existing safety data for the product will also be considered a post-authorization safety study’. In theory, this could then include the large ‘Phase IIIb’ clinical trials usually conducted to evaluate new indications, formulations or methods of administration (i.e. outside the terms of an approved SPC), which would presumably be otherwise covered by the requirements of the Clinical Trials Directive. Hence, companies are advised to clarify their own understanding of the definition of a PASS, if necessary with the assistance of legal advice.

**Regulatory requirements** For each PASS, companies should interact with relevant member state authorities as follows:

- discuss the draft protocol at an early stage;
- submit for comment a copy of the final protocol and any proposed communications to doctors, at least 1 month prior to initiation of the study;
- inform the authorities when the study has commenced;
- provide interim reports on study progress every 6 months from the time of initiation, or as requested by the authorities;
- provide a copy of the final study report within 3–6 months of study completion.

In addition, companies are expected to comply with ongoing expedited and periodic ADR reporting requirements and submit the findings of the study for publication.

**Electronic communication of safety information**

Several member state authorities have been active in the development of technology for the electronic communication of safety data. In 1999, the EMEA, in collaboration with member state authorities and the European pharmaceutical industry, initiated a joint pilot for the electronic communication of ICSRs in accordance with ICH recommendations. This activity has culminated in the production version of the EudraVigilance system, which should facilitate a single standard for the electronic communication of safety data within the EU. The EMEA issued a policy paper in January 2002 (EMEA/H/5255/01) specifying the activities and schedule for rapid implementation of the electronic transmission of ICSRs within the EU. These include the following measures:
• Initiation of electronic transmission of ICSRs amongst member state authorities from 5 December 2001.

• Implementation of electronic transmission from pharmaceutical companies to member state authorities and/or EMEA utilizing EudraVigilance, with pre-coding of ICSRs using current versions of MedDRA and the EudraVigilance product dictionary; this was due to take effect on a mandatory basis from 31 January 2003, but delays have occurred due to technical issues, which should be resolved by end of 2003.

• Completion of migration of legacy data for all medicinal products sold within the EU from pharmaceutical companies to EudraVigilance; this was due to be completed by 31 January 2004, but delay will also occur due to technical issues.

In addition, the EC has issued the ‘SUSAR database’ guideline, in support of the Clinical Trials Directive, that indicates that the EudraVigilance database will eventually contain a ‘Clinical Trials’ module to accommodate SUSAR case reports from clinical trials.

Compliance concept paper
In November 2001, the CPMP issued the ‘Position paper on compliance with pharmacovigilance regulatory obligations’, effective from January 2002. This paper sets out the legal basis for pharmacovigilance obligations in the EU, how compliance should be monitored and the types of regulatory action that may be considered in the event of non-compliance.

The paper indicates that member state authorities will be required to conduct more frequent inspections of companies’ pharmacovigilance capabilities, and that these inspections will be random, systematic and targeted to facilitate, as well as to enforce, compliance with regulatory requirements.

The paper indicates that the following will be regarded as ‘serious’ non-compliance:

• failure to notify changes in benefit–risk profiles
• deliberate non-compliance
• failure to improve, in response to inspection findings and recommendations.

The actions that can be taken by member state authorities will include:

• education and facilitation, with advice on how to remedy non-compliance
• repeat inspections
• formal warnings
• ‘naming and shaming’ of serious/persistent non-compliant companies
• formal caution, if a non-compliant MAH admits that a criminal offence has occurred
• prosecution of serious/persistent non-compliant companies, including their directors, managers or the qualified person responsible for pharmacovigilance.
The United Kingdom

Legal and regulatory basis

The legal basis for UK regulations governing the conduct of pharmacovigilance and notification of safety information within the UK is provided by the Medicines Act 1968, which provides the power to make regulations using statutory instruments (SIs). The Medicines (Exemption from Licences) (Clinical Trials) Order 1995 (SI 1995/2808) and Medicines (Exemption from Licences and Certificates) (Clinical Trials) Order 1995 (SI 1995/2809) currently provide the basis for ADR reporting requirements associated with the conduct of investigational clinical trials within the UK although these will soon be superseded by SIs used to implement the requirements of the ‘Clinical Trials Directive’, at which time the Clinical Trial Certificate (CTC) and Clinical Trial Exemption (CTX) schemes will cease to function.

The Medicines for Human Use Regulations (SI 1994/3144) relate to medicinal products marketed within the UK. It cross-references relevant EC provisions and specifies reporting requirements for pharmaceutical companies relating to the notification of ADRs to the MCA, now known as the MHRA (Medicines and Healthcare products Regulatory Agency). More recently, SI 236/2002 transposed Commission Directive 2000/38/EC into UK law, thereby bringing the UK’s ADR reporting requirements into full accordance with EU legislation.

SI 1994/3144 (Schedule 3) also created a series of criminal offences relating to failure to comply with the legal provisions governing pharmacovigilance and ADR reporting in the UK. Persons found guilty of such offences may be liable to large fines and/or terms of imprisonment. Although the offences apply to the ‘person placing the medicinal product on the market’, it is evident that some are also applicable to the UK company’s qualified person and/or senior management.

The MCA/MHRA have provided guidance within various Medicines Act Leaflets (MAL) and Medicines Act Information Leaflets (MAIL). Although only guidelines, they do represent the agency’s interpretation of UK and EU provisions for the conduct of pharmacovigilance. Hence, compliance with the guidance should minimize risk of indictment or conviction of any offence under Schedule 3 of SI 1994/3144.

Adverse drug reaction reporting requirements for investigational products

Expedited reports

Sponsors of clinical trials are required to notify relevant safety information to the MHRA’s Licensing Division, whether as expedited or periodic reports. It is apparent that this division relies on sponsors to limit their expedited notifications to serious unexpected suspected ADRs (i.e. clinically important cases), and to provide (relatively) less important safety information in annual reports.

With effect from 1995, UK expedited reporting requirements, for medicinal products under clinical investigation within the UK, have been in full accordance with ICH E2A requirements. However, it is possible that some aspects may change with implementation of the Clinical Trials Directive in 2004.

Expedited reporting requirements apply to all serious unexpected ADRs occurring in association with an investigational product covered by a CTC or CTX, regardless of source
or country of origin. The term ‘investigational product’ applies to all new chemical entities, as well as to marketed drugs being evaluated for new indications, formulations, etc.

Further to guidance issued in MAL 4 and MAIL 105, the general understanding is that:

- the 7- and 15-day time frames start on the date that the company is informed about any serious unexpected ADR on a worldwide basis;

- treatment codes should be broken prior to the expedited notification of serious unexpected ADRs from blinded clinical trials; the code break should occur at the time of receipt of information on a case report;

- case reports involving placebo do not require expedited notification.

All AEs that occur in a clinical trial conducted under a CTC or CTX should be subject to causality assessments – all cases qualify as suspected ADRs where the clinical investigator or sponsor considers that there is a ‘reasonable possibility’ of a causal relationship with the investigational product. Guidance in MAL 4 indicates that the MHRA considers that the expression ‘reasonable causal relationship’ is meant to convey that there is a rationale, based on facts or other evidence, to suggest that a causal relationship exists.

In addition to the minimum requirements for expedited reporting specified within ICH E2A, each submission needs to be clearly identified as an ADR report from a clinical trial and include the CTX number, protocol number and company reference number. Reports lacking such information will be returned for completion and resubmission by the company. All clinical trials case reports, whether of UK origin or not, should be submitted on the Clinical Trials Unit’s variation of the ‘Yellow Form’, as specified in MAL 4.

**Periodic reports**

Guidance contained in MAL 4, MAIL 88 and MAIL 105 indicates that companies are required to monitor and keep records of all AEs occurring during a clinical trial conducted under a CTC or CTX. The following should be reported in summary tabulations, either at the conclusion of the trial or at the time of updating or renewal of the CTX (if they occurred within the UK), or with the MAA (if from abroad):

- deaths
- serious expected ADRs
- non-serious ADRs
- withdrawals due to ADRs.

Comment should be included as to the relationship of the events to the pharmacological effects of treatment on the patient population receiving the trial drug. The report may also indicate any instances of significant lack of efficacy, and any new pre-clinical findings that are significant and/or have had an impact on the studies being conducted under the CTX.
**Data Safety Monitoring Boards**

The MHRA encourages companies to appoint a Data Safety Monitoring Board (DSMB) for any clinical trial that involves a patient population with a high mortality disease state, although this is not a mandatory requirement. The expectation is that this committee would:

- decode trialists’ reports
- construct the group sequential analysis
- report ADRs directly to the MHRA using line listings, at agreed time intervals.

Reports submitted by the DSMB should discuss any clinically important difference in the rate of serious AEs between the investigational product and comparator(s), although a formal frequency analysis may not need to be performed. In addition, serious unexpected ADRs should still be reported by the sponsor to the MHRA in accordance with the ICH E2A guideline.

Arrangements for establishing and reporting the line listings, and other safety information, should be defined within each trial protocol. The procedures for this form of reporting may be discussed with the MHRA Clinical Trials Unit in advance of the protocol being finalized, although there is no indication that this is mandatory.

**Adverse drug reaction reporting requirements for marketed products**

It is evident that the MHRA’s strategy for ADR reporting has been based upon full and prompt implementation of relevant EU legislation and the guidance provided within the Pharmacovigilance Guidelines. In addition, the MHRA has been a leading proponent of requirements relating to post-authorization safety studies.

**Expedited reports**

Although the guidance provided within MAIL 87 refers only to spontaneous ADR reports and reports from post-marketing (safety) studies, the UK expedited reporting requirements for marketed products apply to ADRs that arise from any source, if related to the product’s approved marketed use – this also includes relevant ADRs from Phase IV clinical trials and the published literature.

The UK’s expedited reporting requirements are in full accordance with the requirements specified within Council Regulation 2309/93 and Commission Directive 2000/38/EC. However, as published in MAIL 130 (April 2002), the MHRA has requested that MAHs continue to notify all serious ADRs arising from within the EU for any medicinal product subject to the UK’s ‘Black Triangle’ scheme, until such time that electronic reporting into the EudraVigilance system becomes fully operational.

The MAH is also expected to inform the MHRA without delay if any new information is received which may adversely affect the benefit–risk evaluation of the medicinal product. In all instances, expedited reports should be submitted to the MHRA within 15 calendar days of initial receipt of information by the MAH – the MHRA have indicated (informally) that this applies once the information has been received by the UK company or by any of its overseas businesses (parent company or affiliates).
Expedited reports should be submitted to the MHRA using the ‘Yellow Form’. This form should be used for the notification of ADRs from the UK and other EU member states; although the MHRA would also prefer that this form is also used to notify ADRs from non-EU sources, it will accept such reports on a CIOMS I form.

**Periodic safety update reports**

PSURs are required for all medicinal products sold within the UK, regardless of when they were first licensed or the authorization procedure used, with a periodicity for submission in accordance with that specified in Council Directive 2001/83/EC.

In general, the format and content of each PSUR should be consistent with that specified within the ICH E2C guideline. However, guidance provided in MAIL 101 indicates that the MHRA have some specific requirements:

- The timing of submission should be based on the date of first marketing authorization for the product, granted to *any company* in *any country*; after UK marketing authorization approval, the relevant PSURs should be submitted to the MHRA as and when they become available.

- The section on worldwide marketing authorization status should contain information on the dates of renewal as well as dates of marketing authorization.

- Line listings should include the following:
  - cases selected in accordance with ICH E2C criteria, plus
  - non-serious listed ADRs, as an addendum.

- Summary tabulations should be presented for serious and non-serious, listed and unlisted ADRs.

- A comment should be provided for any differences that exist between the CCDS and the UK Data Sheet/SPC, together with their consequences for the overall safety evaluation.

With regard to the addendum containing the line listing of non-serious listed ADRs, the guidance contained within MAIL 101 does not specify whether this applies to all non-serious listed ADRs (i.e. including those from clinical trials, named-patient use and other regulatory authorities), or whether it can be limited to non-serious listed ADRs from spontaneous reports and published literature. A reasonable assumption is that the latter situation should prevail, as most company post-marketing safety databases do not contain non-serious ADRs from clinical trials.

In addition, the MCA indicated in MAIL 101 that it ‘would appreciate a more proactive approach from companies’, with companies paying particular attention to the analysis of data presented in the PSUR. Hence, they suggested that the conclusion of each PSUR should cover the action required to investigate emerging safety signals, together with proposals for amending and updating the marketing authorization and product information in the light of the findings of the PSUR and cumulative experience.
Post-authorization safety studies

The MHRA is a strong advocate of the concept of post-authorization safety studies, as one of the five parties that contributed to the Safety Assessment of Marketed Medicine (SAMM) guidelines issued in 1993, which then formed the basis for the EU’s provisions in this regard. Guidance issued in MAIL 87 and MAIL 104 indicates that they expect pharmaceutical companies to comply with these obligations – this will probably be supplemented by SIs implementing Council Directive 2001/83/EC, now that it provides a formal legal basis for provisions relating to post-authorization safety studies.

It is apparent that the requirements are not restricted to studies conducted within the UK, in that they may apply to any company-sponsored PASS conducted worldwide if it relates to a product authorized in the UK. In addition, MAIL 104 indicates that the company should actively seek information about the study objectives, design, time frame and results if it becomes aware of a relevant study planned or being performed in the UK by a third party, and inform the MHRA accordingly.

ADROIT Electronically Generated Information Service

For several years, the MHRA has been a strong advocate of electronic transmission of safety information. This includes the development of the ADROIT Electronically Generated Information Service (AEGIS).

The MHRA receives over 80 per cent of its ADR reports directly from UK healthcare professionals via the ‘Yellow Card’ scheme. In accordance with EU legislation, it is important that the agency is able to pass on information from this source to MAHs to augment their own understanding of the safety profile of products that they have on the UK market. Hence, AEGIS was introduced in 1993 to facilitate the electronic exchange of information between the pharmaceutical industry and the MHRA.

AEGIS provides companies with (restricted) on-line access to anonymized data on the ADROIT database. For a nominal sum, a company may be granted access to the following information on the ADROIT database:

- Drug Analysis Prints – summary prints of any drug substance marketed within the UK
- Product Analysis Prints – summary prints of the company’s own medicinal products
- Anonymized Single Patient Prints (ASPPs) for any drug substance marketed by that company
- Reaction Analysis Prints (listing of drug substances associated with a particular reaction term)
- Fatal reports (cumulative analysis of the cause of death in ADR reports for a specific substance)
- *Ad hoc* query service.

AEGIS allows the MHRA to meet its obligation to supply information on serious ADRs to
pharmaceutical companies. ASPPs for serious and non-serious reports are made available to AEGIS users on a weekly basis; companies with access to AEGIS then have the responsibility of accessing the database at regular intervals to obtain the information. In addition, the MHRA continues to send ASPPs as paper prints by post every 2 weeks to companies that do not have access through AEGIS (MAIL 87).

**Reporting requirements for marketed products still under clinical investigation**

There remains some ambiguity with regard to the reporting requirements for medicinal products that are marketed within the UK but which are still subject to clinical investigation. The MHRA has previously indicated that new chemical entities and marketed drug substances that are subject to clinical investigation for new indications, formulations or routes of administration qualify as investigational products within the UK. Hence, ADRs that arise from clinical studies conducted within the remit of the UK Data Sheet/SPC (i.e. Phase IV clinical trials or PMS studies) should be notified to the Post-Licensing Division in accordance with the guidance specified in MAIL 87. ADRs that arise from clinical studies on investigational products should be notified to the Clinical Trials Unit in accordance with the provisions of MAIL 88.

**France**

**Legal basis and regulatory framework**

In general, the French ADR reporting requirements are consistent with those mandated by EU legislation and guidelines. It is evident that the Agence Française de Sécurité Sanitaire des produits de Santé (AFSSAPS) has adopted a pragmatic attitude to ADR reporting, thereby facilitating international harmonization of requirements. However, there are two French idiosyncrasies that require specific consideration, namely protocol-related events and imputability assessments (see below).

The French ADR reporting requirements for investigational products are defined by the Loi Huriet (22 December 1988), which concerns all forms of trials and medical experiments on living human beings in France, specifically Article (L1123-8) du Livre II bis du Code de la Sante Publique. The law is applicable to all biomedical research and aims to protect all subjects participating in clinical investigations.

Detailed requirements for the reporting of adverse events from clinical trials are currently specified in two guidelines, ‘Recommendations du 12 Septembre 1994’, issued by the AFSSAPS, and ‘Recommendations for the reporting of serious events likely to be attributable to research’, issued by Syndicat National de l’Industrie Pharmaceutique (SNIP) on 21 February 1997. Although draft legislation was issued in March 2003, amending the Loi Huriet in order to implement the Clinical Trials Directive, at the time of writing it is not known what changes, if any, will occur in response to implementation of the Clinical Trials Directive.

With regard to marketed products, the French government issued Decree No. 95-278 on 13 March 1995, modifying the Code de la Sante Publique and thereby implementing Council Directive 75/319/EEC (as amended). This is supported by a guideline from the AFSSAPS (‘Notification of Adverse Reactions’), issued by SNIP on 18 October 1996.
Definitions

For marketed products, the AFSSAPS has applied definitions consistent with EU legislation and regulations. However, the definitions used for the notification of ADRs from clinical trials differ slightly from those in use for marketed products, most notably with regard to protocol-related events and the definition of a serious AE.

Protocol-related events

An adverse event is defined as any noxious and new medical condition occurring during the conduct of a clinical trial, whatever its cause; this specifically includes events that occur during diagnostic procedures and the washout phase of any study. Likewise, an adverse reaction is defined as any event due to the study conduct, i.e. it may relate to the design of a trial and need not be related to the study drug.

Hence, all AEs that occur during a clinical trial and cannot be related to a cause independent of the trial conditions are considered as protocol-related events. This is relevant, as such events may qualify for expedited notification to the AFSSAPS even if clearly not drug related.

Foreign patients are included in this requirement when the trial is multinational and involves French centres. This means that companies operating outside France need to be aware of which trials involve French centres.

Serious adverse events

Within the context of clinical trials conducted in France, an AE is considered as ‘serious’ if, in addition to the widely accepted (ICH) criteria, it meets one or more of the following criteria:

- is judged as serious in a clinical sense by either the investigator or sponsor
- is a clinically important laboratory abnormality
- is specified within the trial protocol as a serious AE (regardless of clinical outcome)
- is from the list of WHO critical terms.

Although these additional criteria appear unique to France, they all probably fall within the ICH concept of ‘medically important’ events and, hence, should have minimal impact upon working practice in those companies that utilize the ICH definition.

General requirements for pharmaceutical companies

In addition to the general requirements specified within the Pharmacovigilance Guidelines, any company marketing a medicinal product within France must inform the AFSSAPS of the name of the designated person responsible for pharmacovigilance within the company, who must be a physician or a pharmacist. Article R 5144-17 of the Code de la Sante Publique states: ‘Every company or organization exploiting a medicine … must have a pharmacovigilance department. The name of the person responsible for this department,
medical doctor or pharmacist, must be communicated to the Drug Agency by the Responsible Pharmacist of this company or organization’.

Investigational products

French expedited reporting requirements for investigational products are generally consistent with ICH E2A, although it is possible that some details could change with implementation of the Clinical Trials Directive in 2004.

The AFSSAPS requires that the following be notified as expedited reports:

- fatal or life-threatening unexpected events – preliminary notification within seven calendar days of initial receipt of information by the sponsor, with a written report within a further eight calendar days (if the 7-day report is incomplete);

- all other serious events – written report within 15 calendar days from initial receipt of information by the sponsor.

The events that qualify for expedited reports also depend on their country of origin:

- French cases – all serious adverse experiences that are potentially related to the clinical research, i.e. study drug, active comparator, placebo or protocol-related;

- foreign cases – all serious adverse experiences that are potentially due to the clinical research (as above) when a multicentre trial involves French sites, plus all serious unexpected ADRs (i.e. only related to the study drug) when the trial is conducted abroad and lacks French centres.

In addition, companies are required to notify the AFSSAPS within 15 calendar days of acquiring any new information that can decrease the benefit–risk ratio for the subjects participating in a trial. This includes:

- serious unexpected ADRs from spontaneous reports, published literature, other regulatory agencies and foreign trials;

- results from interim analyses concerning safety or lack of efficacy;

- increased incidence of serious AE/ADRs in special groups;

- discontinuation of other clinical trials;

- new safety information arising from pre-clinical studies.

The AFSSAPS has not decreed that the study drug must be identified prior to expedited reporting. Companies may maintain the study ‘blind’ if they wish and submit reports to the AFSSAPS as ‘code unbroken’. However, the AFSSAPS should then be notified of the drug’s identity once the ‘blind’ has been broken at the end of the study.

Companies are required to use a local form (CERFA Form 65-0040) for the expedited notification of cases arising in France; foreign cases may be submitted using the same form or a modified CIOMS I form. In addition, the French law requires companies to notify
relevant facts to ethics committees, although it appears that this seldom happens in practice. Periodic reports are not required for investigational products within France.

**Marketed products**

*Expedited reports*

In full accordance with EU legislation, the following have to be notified to the AFSSAPS within 15 days of receipt of information by the company worldwide:

- serious ADRs occurring in France
- serious unexpected ADRs from non-EU countries.

However, companies may also notify serious suspected ADRs that have come from other EU member states, although this is not a mandatory requirement.

If a serious ADR leads to an expedited modification of a French SPC, then the company involved should inform the AFSSAPS by telephone at the same time that the dossier supporting the amendment is sent by mail.

Companies are required to conduct a formal causality assessment of all serious ADRs that originate in France prior to notification to the AFSSAPS. The assessments are mandatory for all French cases, but are optional for foreign cases, and must use the official French imputability method as defined by Begaud et al. (1985). This combines chronological and semiological criteria, and results in the ranking of the suspect drug at one of five levels of causality.

*Periodic safety update reports*

The AFSSAPS has stipulated that PSURs should be produced in full accordance with the content, format and periodicity specified in the Pharmacovigilance Guidelines.

In addition, for products registered under French national procedures, companies should submit information on the French experience during the period under review, for the purpose of comparison with the international experience. The information required on French cases in this additional report includes:

- number of cases reported;
- summary table of ADRs classified by nature and imputability to drug;
- number of ‘serious’ case reports;
- serious ADRs classified as ‘unexpected’ with reference to the French SPC;
- evaluation of the number of patients treated in France;
- conclusion, including a comparison with the previous situation and implications for the French SPC.

The AFSSAPS has indicated that companies having to satisfy international periodic reporting requirements, may present PSURs made up of 6-month units, with a global evaluation of the
period covered by the report. In addition, manufacturers may consult with the AFSSAPS in order to agree birth dates that would be mutually acceptable to both parties.

**Germany**

**Legal basis and regulatory framework**

The German Drug Law (AMG), most notably Sections 29(1) and 49, provides the legal basis for current German ADR reporting requirements. This covers the manufacturers’ obligations relating to the conduct of pharmacovigilance, expedited and periodic reporting and the graduated plan (Stufenplanverfahren). The 3rd Promulgation (May 1996) on the Notification of Adverse Reactions, Interaction with Other Products and Drug Abuse, produced by the Federal Institute for Drugs and Medical Devices (BfArM) and the Paul-Ehrlich Institut for Sera, Vaccines and Blood Products, provides the German authorities’ interpretation of the AMG.

The AMG specifies a series of offences and penalties for non-compliance with its requirements. For example, there is an administrative offence relating to non-compliance with the requirements of Section 29(1) that may incur a large personal fine for the Stufenplanbeauftragter (see below). In addition, the Stufenplanbeauftragter may also be liable to criminal prosecution for bodily injury or involuntary manslaughter.

**Definitions**

The BfArM has adopted most of the relevant ICH definitions and those stipulated by EU legislation. However, the 3rd Promulgation introduced some variation, providing some definitions that appear applicable only in Germany, as presented below.

**Adverse reaction**

In addition to the definition provided by Council Directive 2001/83/EC, the BfArM considers that an ADR should be suspected if an AE meets two other criteria:

- the event has a temporal association with administration of the product (including an allowance for the possibility of delayed effects), and
- the event has evidently not been brought about by any cause other than administration of the drug.

All events attributable to causes other than administration of the drug should be considered as unrelated to the drug. This includes symptoms due to a patient’s underlying disease or concurrent disease, although deterioration of a patient’s symptoms should be evaluated to determine whether this has been due to natural disease progression or caused by the drug.

**Lack of efficacy**

Occurences of lack of efficacy should be treated in the same way as conventional ADRs when the lack of efficacy is considered to have damaged the patient’s health. This is
especially so when associated with drug interactions or insufficient efficacy of sera, vaccines, blood preparations, test allergens, test sera and test antigens.

**Serious adverse event**

The BfArM has clarified two aspects of the definition of a serious AE:

- the term ‘unexplained death’ should be used to describe the event when the cause of death cannot be determined;

- the term ‘disability’ applies when the patient has suffered considerable disability or permanent damage, including, in particular, the inability to work as a result of lasting damage to health.

**Healthcare professionals**

German regulations require that ADRs should be confirmed by healthcare professionals in order to qualify for notification to BfArM, although BfArM will accept consumer reports if they are of clinical importance and have been evaluated by the Stufenplanbeauftragter.

The 3rd Promulgation indicates that non-medical practitioners (Heilpraktiker) and psychotherapists qualify as healthcare professionals in Germany, in addition to those specified within the Pharmacovigilance Guidelines.

**Commissioner for the Graduated Plan (Stufenplanbeauftragter)**

Any company marketing a medicinal product in Germany must appoint a Commissioner for the Graduated Plan (Stufenplanbeauftragter). The individual must be qualified in human or veterinary medicine or pharmacy and should have an appropriate level of knowledge and reliability necessary for the collection, evaluation and notification of ADR reports, and coordination of any measures that might be required consequent to any changes to the company’s product safety profile. The company is required to notify the name of this individual, and any changes in personnel thereafter, to the local German authority.

The Stufenplanbeauftragter has personal responsibility for ensuring that their company complies with the relevant parts of the AMG, and is personally liable for meeting any fines in the event of an administrative offence.

**Expedited reports**

German expedited reporting requirements are currently identical for investigational and marketed medicinal products, although, at the time of writing, it is not known what changes (if any) will occur with regard to investigational products as a result of implementation of the Clinical Trials Directive.

At present, unlike the rest of the EU, all serious ADRs qualify for expedited reporting to the BfArM, within 15 days from the date of initial receipt by the German company/affiliate, whether they originate from a clinical study or from post-marketing use, and regardless of the country of origin. The only exceptions relate to:
• ADRs associated with medicinal products authorized under the EU’s centralized procedure – these require notification in accordance with the case selectivity specified by Council Regulation 2309/93;

• ADRs cited in the scientific literature – single case reports should be notified to the BfArM within 15 days if they are serious and unexpected.

German and foreign cases may be notified in German or English, either using a specific German form, the ‘Bericht uber unerwunschte Arzneimittelwirkungen’ (‘Adverse Drug Reaction Report’), or a CIOMS I form.

**Reporting requirements before marketing authorization**

The requirement for the expedited notification of reports for investigational products depends upon the German registration status of the product. Reports should be submitted prior to submission of an MAA simply for the purpose of registration with the BfArM, whereas, following submission of the MAA, cases should be notified expeditiously if they are considered relevant to the ongoing evaluation of the submission.

Hence, prior to submission of the dossier, serious ADRs should only be sent as expedited reports to the BfArM if they arise from clinical trials conducted in Germany or international clinical trials that have centres in Germany. Once the submission has been filed, then serious ADRs of foreign origin should be notified, whether arising from post-marketed use or clinical trials that do not have German centres, in addition those of German origin.

**Minimum criteria for expedited reports**

Although case reports should contain at least the minimum information specified within the Pharmacovigilance Guidelines, the BfArM has indicated that expedited reports are still required should follow-up of serious unexpected ADRs that lack specific patient identification (e.g. ‘in several patients’, ‘in x per cent of patients’) not result in further detailed information.

**Management of adverse drug reactions from ‘blind’ clinical trials**

The 3rd Promulgation indicates that randomization codes should be broken prior to notification of ADRs that arise from ‘blinded’ clinical trials. However, the guidance does not explicitly state that the ‘blind’ must be broken at the time that the German company receives information on a serious ADR. Instead, it indicates that the period for immediate notification commences with the breaking of the blind.

In practice, it is apparent that BfArM expects companies to break the blind for serious unexpected ADRs on an immediate basis and report these accordingly. However, companies may elect to defer the code break for serious expected ADRs until completion of the trial and its database lock, with an expectation that expedited notification will occur within 15 days of the eventual code break.
Scientific evaluations

All expedited reports, regardless of their country of origin, are subject to ‘scientific evaluation’ prior to submission to the BfArM. Each evaluation should include:

- the case description;
- assessments of causality and expectedness, and whether the status of scientific knowledge regarding the product has changed;
- evaluation of whether measures are required with regard to the approval status of the product or reduction of the risk to other patients.

Drug abuse and misuse

The AMG places a significant emphasis on the need for companies to report drug abuse, defined as the deliberate maladministration of a drug, especially when associated with damage to human health. Companies should notify all known instances of frequent abuse or significant abuse in a single individual, if the abuse may (directly or indirectly) endanger human health.

The 3rd Promulgation specifically indicates that AE occurring in association with off-label use should be managed in the same manner as ADRs that occur during licensed use of the drug.

Periodic safety update reports

Periodic safety updates are not required for investigational products.

For products licensed in Germany, PSURs should be submitted, in English or German, in the same time frame as that used elsewhere within the EU. However, the ‘clock’ is often reset in any circumstance that requires renewal of the marketing authorization, most notably approval of a new indication (even for a well-established ‘mature’ product).

Although the BfArM has indicated that the schedule for submission should be based on the German date of marketing authorization, it allows German MAHs to submit their initial PSURs early so that the schedule can then be synchronized with that determined by the EU birth date.

Strict interpretation of Section 29 of AMG requires that a PSUR should include all ADRs notified to the company during the period under review. In practice, the BfArM accepts PSURs produced in accordance with the Pharmacovigilance Guidelines, supplemented with a line listing of non-serious expected ADRs.

In addition, PSURs submitted to the BfArM should include a section focusing on the product’s ongoing safety profile with regard to marketed use in Germany. Current understanding is that this section should highlight differences between the CCDS and the German SPC, and indicate the actions that the German company/affiliate will undertake in response to new information generated within the PSUR.
Experience reports

In addition to PSURs, companies are also expected to submit ‘experience’ reports 2 years and 5 years after initial marketing authorization, in accordance with Section 49(6) of AMG. ‘Experience’ reports should be structured as follows:

- Registration status.
- Details of marketing authorizations in other countries, including conditions of approval and reasons for any withdrawals or rejections.
- German sales data and foreign sales data, plus an estimate of the number of patients exposed.
- List of studies performed, together with copies of all study reports finalized during the reporting period.
- Summary of type and frequency of ADRs.
- Summary and conclusion, with an assessment of any change to the benefit–risk evaluation and justification for any unexpected ADR report that remains absent from the German SPC.

United States of America

Legal and regulatory framework

In the USA, the legal basis for drug regulation, including those governing pharmacovigilance and ADR reporting, is provided by the Kefauver–Harris Amendments (‘1962 Amendments’) to the Federal Food, Drugs and Cosmetics Act of 1938. The 1962 Amendments also provide the FDA with the power to revoke authorization for clinical trials at any time, if it suspects that the drug under investigation is unsafe. In addition, although the amendments do not mandate PMS, the FDA is empowered to require that a manufacturer conducts post-marketing clinical studies as a condition of approval of a New Drug Application (NDA), if it considers that further demonstration of safety is necessary once a product is on the market.

Federal regulations oblige the sponsor of an IND or the manufacturer granted an NDA to report suspected ADRs to the FDA, for all medicinal products sold or being developed in the USA. These are specified in Title 21 of the Code of Federal Regulations, as follows:

- 21 CFR 310.304: ‘grandfathered’ drugs (pre-1938)
- 21 CFR 312.32: IND Safety Reports
- 21 CFR 314.80: post-marketing reporting (drugs) – applicable to medicinal products granted a marketing licence, either as a full NDA or abbreviated application [ANDA]
- 21 CFR 314.98: generic products
• 21 CFR 600.80: post-marketing reporting (biologics) – applicable to licensed biological products (including vaccines).

The Expedited Safety Reporting Final Rule, published in the Federal Register on 7 October 1997 and effective from 6 April 1998, amended the above regulations in order to improve harmonization of US expedited reporting standards with other ICH regions.

In March 2003, the FDA issued a proposed rule, ‘Safety Reporting Requirements for Human Drug and Biological Products’, otherwise known as the ‘Safety Tome’, which proposes significant changes to for pre- and post-approval safety reporting requirements. At the time of writing, the proposals have been subject to extensive review and comment by interested parties, and it is likely that they will not become fully effective before the latter part of 2004.

FDA guidance on ADR reporting is provided in several documents, including:

• Guideline for Post-marketing Reporting of Adverse Drug Experiences (March 1992)

• Guideline for Adverse Experience Reporting for Licensed Biological Products (October 1993)


Federal regulations clearly indicate that ADR reporting requirements are not specific to the US company that holds the IND application or NDA, but also apply to any of its affiliates, these being any corporate entity relating to the applicant, including all subsidiaries, licensees or licensors.

**Food and Drug Administration**

The FDA is responsible for assuring the safety and efficacy of all regulated medical products developed or marketed in the USA, including biological products. Two departments within the FDA bear this responsibility:

• Center for Drug Evaluation and Research (CDER), responsible for monitoring the safety of the majority of drugs sold or developed in the USA.

• Center for Biological Evaluation and Research (CBER), responsible for monitoring the safety of licensed biological products and vaccines.

Safety information on investigational products should be notified to the relevant therapeutic division within the Office of New Drugs. The Office of Drug Safety has responsibility for post-marketing ADR reporting for non-biological products and operates the Adverse Event Reporting System (AERS) database for post-marketing pharmacovigilance purposes. The AERS database also generates compliance reports that enable the Office of Compliance to determine whether companies are submitting reports in accordance with federal regulations. A programme is currently ongoing to develop the methodology for manufacturers to download safety data electronically onto AERS in accordance with ICH standards.
Definitions

Definitions relevant to ADR reporting are provided within 21 CFR Sections 312.32(b) and 314.80(a) for IND applications and NDAs respectively. In general, these are consistent with the corresponding ICH definitions. Those specific to the USA are presented below.

Sponsor

The sponsor is the person or corporate entity that takes responsibility for, and initiates, a clinical investigation, and may be an individual or pharmaceutical company, government agency, academic institution, private or other organization. In practice, the sponsor is the individual/organization that submitted the IND application covering the clinical investigation.

Adverse drug experience

Within the USA, the term ‘adverse drug experience’ (ADE) tends to be used rather than the terms AE or ADR. In practice, an ADE is considered synonymous with an AE. Indeed, FDA guidance on this matter indicates that reporting an ADE does not necessarily reflect a conclusion by the company or the FDA that the event is causally related to the drug.

An ADE is defined as any AE associated with the use of a drug or biological product in humans, whether or not considered to be product related. It includes AEs occurring in the usual course of professional practice (i.e. ‘spontaneous’ reports), as well as those occurring in association with overdose or abuse of a product, whether accidental or intentional. An ADE also includes any significant failure of expected pharmacological action.

Adverse drug reaction

At present, there is no federal definition of an ADR. However, expressions are used in the IND and NDA regulations that are synonymous in their meaning.

Under the terms of an IND, sponsors are required to notify ADEs that are ‘associated with the use of the drug’. This means that there is a ‘reasonable possibility’ that the experience may have been caused by the drug, analogous to the philosophy that has since been adopted by the ICH in its definition of a suspected ADR.

All ADEs notified on an unsolicited basis to pharmaceutical companies or direct to the FDA, by healthcare professionals or consumers, are considered as ‘spontaneous reports’. In the context of federal regulations, all spontaneous reports are regarded as ADRs: the mere act of unsolicited notification implies that the reporter suspects that a causal relationship exists.

Serious adverse drug experience

As of 6 April 1998, the FDA formally adopted the ICH definition of a serious AE and applied it equally to the pre- and post-marketing situations.

The FDA has clarified that the term ‘persistent or significant disability’ equates with a substantial disruption in a person’s ability to conduct normal life functions.

With regard to the ‘important medical event’ criterion, the FDA's MedWatch programme
has simplified this to ‘requires intervention to prevent permanent impairment or damage’. Under IND regulations, a serious ADE also includes any experience suggesting a significant risk for human subjects, including any finding of mutagenicity, teratogenicity or carcinogenicity with respect to results obtained from pre-clinical testing.

**Unexpected/unlabelled adverse drug experience**

The terms ‘expected’ and ‘labelled’ tend to be used interchangeably within the USA, as are ‘unexpected’ and ‘unlabelled’. Although the IND and NDA definitions of ‘unexpected’ relate to different reference documentation, they are consistent in that they both refer to the specificity or severity of the event in the reference documents. However, whilst the IND definition of ‘unexpected’ is consistent with that provided by the ICH, under the terms of an NDA, an ADE is regarded as ‘unexpected’ simply if it is not listed in the current Professional Information Brochure (PIB) for the product.

Federal regulations also clarify that the term ‘unexpected’ refers to an ADE that has not previously been observed during the use of the product, rather than from the perspective of such an experience not being anticipated from the product’s pharmacological properties. In addition, an observed event does not necessarily equate with an ‘expected’ event: its frequency and severity need full characterization before it can be considered as ‘expected’. This is clarified by the Federal Register, which indicates that ‘a sponsor would be required to report each successive case of a serious and unexpected adverse experience until the risk posed by the experience is sufficiently well understood to be described in the Investigator’s Brochure or until an equally satisfactory resolution of the issue is reached (for example, a determination that the experience is not drug related)’, i.e. a serious ADR that had been reported previously could still be regarded as ‘unexpected’.

The 1992 guideline on post-marketing reporting indicates that class-related effects should be considered as ‘unexpected’ if they are not mentioned with specific regard to the product within its label. For example, a rash should be considered as unexpected even if the label refers to ‘Rash may be associated with this class of antibiotics’, when it lacks a specific reference to the occurrence of rash from the product itself.

**Interpretation of Food and Drug Administration guidance on reporting deaths**

Although there is no specific reference to death in relation to ‘unexpectedness’ in the IND or NDA regulations, the FDA issued guidance on this topic in its 1992 guideline on post-marketing reporting. Although issued with regard to NDA reports, it can be assumed that this guidance also applies to IND reporting.

The guideline indicates that death is ‘unlabelled’ (i.e. ‘unexpected’) when labelling does not specify that the event may be associated with a fatal outcome. The guideline indicates that the FDA expects to be notified about all ADRs that have a fatal outcome, even when the cause of death is unknown. Manufacturers and sponsors only need to determine whether notification occurs on an expedited or periodic basis, the primary consideration being the ‘expectedness’ of the fatal outcome.

However, the guideline oversimplifies the clinical relevance of a fatal outcome and disregards the clinical context within which that fatality occurs. Hence, companies must decide for themselves the extent to which they will act in accordance with this guidance.
Reporting requirements for investigational products

IND regulations require that the sponsor shall promptly review all information relevant to the safety of the drug obtained or otherwise received from any source, foreign or domestic. Sponsors are required to notify ADEs that are associated with the use of the drug and have a reasonable possibility of a causal relationship (i.e. suspected ADRs), either as expedited or as periodic reports, dependent upon the nature of the ADE.

Investigational New Drug safety reports

Consistent with ICH E2A, expedited reports (‘IND safety reports’) are required for the following:

- all serious unexpected ADRs associated with the use of the investigational drug product, regardless of source, including trials not covered by the IND and post-marketing use, or country of origin;
- any significant finding from pre-clinical tests, including reports of mutagenicity, teratogenicity or carcinogenicity.

The only qualification relates to the time allowed for the sponsor to notify the relevant division of CDER or CBER:

- 7 days (via telephone/fax) – fatal or life-threatening unexpected ADRs, to be followed by a written report within a further 8 days;
- 15 days (written report) – other serious unexpected ADRs and significant pre-clinical findings.

The 7-day reports need only be notified to the FDA. However, all 15-day reports should be sent simultaneously to the FDA and investigators covered by the IND.

There is no need to notify ADRs that occur in association with administration of placebo. If an active comparator is involved, then ADRs should be notified either to the FDA or manufacturer of the comparator. In the latter instance, it is the responsibility of the receiving company to assess whether the ADR is ultimately reportable to the FDA.

All relevant follow-up information relating to a previously submitted IND safety report should be notified to the FDA as soon as the relevant information becomes available. If the results of the follow-up establish that an ADE initially considered as non-reportable has become reportable under the provisions of an IND, then the sponsor is required to send an IND safety report to the FDA within 15 days of making such a determination.

Each written notification should be submitted as follows:

- domestic case – Form 3500A or in a narrative format;
- foreign case – Form 3500A or CIOMS I form, or in a narrative format;
- results from animal or epidemiological studies – narrative format.
The sponsor should identify all safety reports previously filed under the IND that concern a similar adverse experience, together with an analysis of the significance of the adverse experience in the light of previous, similar reports.

An FDA commentary issued in the Federal Register (7 October 1997) indicates that sponsors should break the ‘blind’ for reportable events that occur during ‘blind’ clinical investigations, at the level of the individual subject/patient in question. It also advises that sponsors should consult with the FDA division responsible for the product’s IND if they are concerned that breaking the ‘blind’ would compromise their study, e.g. when a fatal or other serious outcome is the primary efficacy endpoint in the clinical trial.

Further guidance indicates the following for ADEs that occur in association with products approved for marketing within the USA:

- ADRs that occur during an IND clinical study, relating to a product with an approved NDA, are subject to both IND and NDA reporting requirements; evaluations of ‘expectedness’ should be based on the use of IB and PIB for respective reference purposes.

- ADRs that occur outside an IND study, relating to a product with an approved NDA, are only subject to NDA reporting requirements, even if the product has an ‘open’ IND.

Thus, the only time that an event should be reported to both IND and NDA would be when a serious suspected ADR occurs in an IND study, and the event is classified as ‘unexpected’ on the basis of both IB and PIB.

Investigational New Drug annual reports

The sponsor is required to submit a report on the progress of clinical investigations within 60 days of each IND anniversary. This annual report should include:

- Individual study information – status of each study covered by the IND in progress or completed during the year under review.
- Summary information:
  - most frequent and most serious adverse experiences;
  - all IND (15 day) safety reports submitted during the year under review;
  - list of all subjects who died, with their cause of death;
  - list of subjects withdrawn in association with adverse experiences;
  - brief description of information relevant to the understanding of the drug’s actions;
  - list of pre-clinical studies completed and a summary of major findings;
  - summary of any significant manufacturing or microbiological changes.
- Other information:
  - description of the general plan of investigation for the forthcoming year;
Reporting requirements for marketed products

Each company (the ‘applicant’) having a product cleared for marketing is required to review all ADEs obtained, or otherwise received, from all sources, whether foreign or domestic. Whether through expedited or periodic reports, the following must currently be reported:

- all spontaneous reports of ADEs occurring within the USA (‘domestic’ reports);
- foreign, literature and study reports involving
  - serious unexpected ADEs
  - increased frequency of serious labelled ADEs.

Study reports should only be submitted if there is ‘reasonable possibility’ that the drug caused the ADE, i.e. it is a suspected ADR.

Responsibility for submission of reports also applies to any person or entity whose name appears on the label of a marketed drug as its manufacturer, packer or distributor. However, the regulations do allow the ‘non-applicant’ to discharge responsibility by ensuring that all relevant information is communicated to the applicant within 5 days of its receipt by the non-applicant. However, the non-applicant is then obliged to maintain a record of any such action.

Expedited reports

The applicant must notify to the FDA all ADEs that are both serious and unexpected, regardless of source, within 15 calendar days of the time of initial receipt of information by the applicant. With regard to ADEs from clinical trials or post-marketing studies, the applicant should report only those cases that are serious, unexpected and considered as having a reasonable possibility that the drug caused the event, i.e. serious unexpected ADRs. Although not specifically stated in the regulations, it is apparent that the ‘regulatory clock’ for 15-day reports starts at the time that the applicant receives sufficient information to identify a valid case as ‘serious’. For foreign cases, the ‘clock’ begins when the applicant or its foreign affiliate/HQ has received sufficient data to suggest that the 15-day criteria have been met.

If the initial 15-day report contains incomplete information, the applicant should file a preliminary report pending the receipt of further information. Additional follow-up information should then be sought, at least sufficient to complete a Form 3500A, and submitted to the FDA within 15 calendar days after receipt of any new information. If additional information is not obtainable, then the applicant should maintain records of the steps taken to seek additional information.

Domestic case reports should be notified using the FDA Form 3500A or, for vaccines, a
VAERS form. Foreign cases may be submitted using Form 3500A or a CIOMS I form. Reports may be submitted using a computer-generated format provided that the content is equivalent in terms of the information that would otherwise have been provided on a Form 3500A and that the format is agreed in advance with the FDA.

**Data elements for a post-marketing safety report** The August 1997 CDER/CBER guideline indicates that case reports should meet minimum criteria for reporting, analogous to those specified within ICH E2A, before submission to the FDA. Case reports not meeting this standard should not be submitted to the FDA. If a report is submitted that lacks one or more of the basic data elements, then it will be returned to the reporter marked ‘insufficient data for a report’.

Case reports should contain enough information to indicate that a specific patient was involved. For example, a report stating that ‘an elderly woman had anaphylaxis’ or ‘a young man experienced anaphylaxis’ is acceptable, whereas one that states ‘some patients got anaphylaxis’ does not meet the specified requirements.

The ADE being reported should have some specificity, e.g. one or more signs (including abnormal laboratory findings), symptoms or disease diagnosis. Reports that state, for example, ‘experienced unspecified injury’ or ‘suffered irreparable damage’ should not be submitted until more specific information about the nature of the AE can be determined.

**Scientific literature** Serious unexpected ADEs reported in the scientific literature, either as case reports or as results of clinical study, must be submitted as 15-day reports on a suitable form together with a copy of the article, translated into English if published in a foreign language. A separate Form 3500A should be completed for each identifiable patient.

If the article refers to more than one drug product, then the manufacturer of the ‘suspect drug’ is responsible for submission of the report to the FDA; the ‘suspect drug’ is usually that identified by the article’s author, often within the article’s title.

**Solicited information** The 1997 CDER/CBER guideline indicates that information concerning potential ADEs received during planned contacts and active solicitation of information from patients (e.g. patient support programmes, disease management programmes) are not considered as ‘spontaneous’ reports. They should be handled in the same way as case reports obtained from post-marketing studies, i.e. ADEs should only be submitted if they are serious, unexpected and there is reasonable possibility that the drug caused the event.

**Overdose** Reports of overdose should be submitted only when the overdose was associated with an adverse experience; the ADE would qualify for a 15-day report if it was serious, unexpected and suspected as being drug related.

**Reporting of events on another company’s products** There are no regulated requirements for sponsors of clinical trials to notify ADRs that occur with active comparator agents on an expedited basis to the FDA. However, the FDA has indicated that sponsors should choose to notify serious unexpected ADRs that occur in patients given active comparators either to the relevant regulatory authorities or to the manufacturer of the product concerned.

With regard to marketed products, the 1992 guideline indicates that the recipient of
reports of serious unexpected ADRs that occur in patients administered products subject to another company’s NDA should notify the product’s manufacturer, not the FDA.

**Periodic reports**

Periodic reports are due on a quarterly basis during the first 3 years after NDA approval and annually thereafter. If there is a delay between the granting of a licence and initial marketing within the USA, then quarterly reports will be required for the first 3 years after initiation of marketing. Federal regulations also allow the FDA to extend the time over which quarterly reports should be submitted, e.g. after the submission of a major supplemental NDA.

Quarterly reports must be submitted to the FDA within 30 calendar days of the last day of the reporting quarter. Annual reports must be submitted within 60 calendar days of the anniversary date of NDA approval.

Cases that qualify for inclusion in the report are summarized in Table 9.7.

<table>
<thead>
<tr>
<th>Source</th>
<th>Type of case report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous reports</td>
<td>All domestic ADEs (serious and non-serious)</td>
</tr>
<tr>
<td>Published literature</td>
<td>Serious unexpected ADEs</td>
</tr>
<tr>
<td>Clinical trials and PMS studies</td>
<td>Serious unexpected ADRs</td>
</tr>
</tbody>
</table>

In addition, all domestic spontaneous reports of ‘lack of effect’ (i.e. failure to produce the expected pharmacological effect) should be submitted in the periodic report with other domestic ADEs. However, reports of ‘lack of effect’ do not require notification to the FDA if from abroad and/or associated with an unapproved indication.

The FDA has specifically indicated that the following cases do not need to be submitted as part of a periodic report:

- domestic serious unexpected spontaneous ADEs (as they should already have been notified as 15-day reports);
- foreign marketing experience (except serious unexpected ADEs);
- ADEs from post-marketing studies, except serious unexpected ADRs;
- ADE reports within the scientific literature, except serious unexpected ADEs.

Each periodic report should contain four sections arranged in the following order:

1. Form 3500As – for each serious expected and non-serious unexpected spontaneous report.
   The 1997 CDER/CBER guideline indicates that the FDA will issue a waiver for the requirement to submit Form 3500As for non-serious expected case reports, upon specific request by the applicant.

2. Line listing of Form 3500As submitted in Section 1.
For any drug interaction listed as an ADE, the interacting drugs should be identified in this line listing.

3. Narrative summary and analysis of information in the periodic report, as well as an analysis of the 15-day reports submitted during the reporting period. This section should include:

- a listing of the 15-day reports submitted during the period under review;
- a listing of all ADE terms and counts of occurrences during the period under review, taken from the 15-day reports of serious unlabelled ADEs notified during the period;
- a summary of ADE reports in which the drug was listed as one of the suspect drugs but the report was filed to another NDA held by the applicant;
- a narrative discussion of the clinical significance of the 15-day reports, assessing the clinical significance and an overall evaluation of the new information received during the period under review relating to that already known about the drug.

4. Narrative discussion of action(s) taken as a result of new safety information, including any labelling changes or studies initiated since the last periodic report, a summary of important foreign actions (e.g. new warnings, limitations in indications and use of the product), any communications of new safety information (e.g. ‘Dear Doctor’ letters) and a copy of the current PIB.

ICH E2C periodic safety update reports The FDA has indicated that it will accept periodic reports in accordance with ICH E2C format and content, provided that the applicant first secures a waiver from the FDA. Current experience indicates that the waiver could be subject to some or all of the following conditions:

- PSURs are prepared in accordance with the ICH E2C guideline, as published in the Federal Register (19 May 1997).

- PSURs are submitted in accordance with the usual periodicity and time frames for US periodic reports, i.e. quarterly reports may still be required for new products, with 30-day deadlines for submission; however, there are instances whereby the FDA will accept PSURs every 6 months for the first 2 years after approval, and annually thereafter, based upon the IBD and all with 60-day deadlines for submission.

- All indications, dosage forms and formulations may be covered in a single PSUR, subject to the following:
  - a copy should be submitted to each approved NDA/ANDA covered by the PSUR;
  - information on different dosage forms, formulations and/or indications should be presented in separate sections, if needed to portray accurately the safety profile of
the product, e.g. do not combine safety information from ophthalmic drop dosage forms with solid oral dosage forms.

- Appendices should be attached, as follows:
  - copies of 3500A forms as required by 21 CFR 314.80(c)(2), including consumer reports;
  - tabular listing of all consumer-reported AE terms and counts of non-serious listed ADRs, if such cases are not already included in the international PSUR;
  - a narrative that references the changes considered as appropriate in the CCDS, as well as any changes considered appropriate to the approved US labelling for the product(s) covered by the PSUR;
  - a copy of the most recently approved US labelling for the product(s) covered by the PSUR.

**Record keeping**

The applicant is required to keep records of all ADEs for 10 years, including raw data and any correspondence relating to ADEs. Manufacturers, packers and distributors are required to permit any authorized FDA employee to have access to, copy and verify such records.

**The ‘Safety Tome’**

On 14 March 2003, the FDA published a 93-page proposed rule to change the requirements associated with pre- and post-approval safety reporting for drugs, biologics, and devices. Significant revisions to existing definitions and reporting requirements are proposed, with a number of new definitions and reporting requirements added, which, if implemented, will have significant practical implications for industry.

An extended period has been allowed for comments by interested parties owing to the length of the proposed rule, with final comments not due to the FDA until October 2003. The final rule will become effective 180 days after its publication in the Federal Register, likely to be in early 2004, although a full year will be allowed for compliance with the requirement for use of the MedDRA coding dictionary.

In summary, the major changes being proposed are as follows:

- New definition for a suspected ADR, to replace the term ‘adverse drug experience’; to be ‘a noxious and unintended response to any dose of a drug product for which a relationship between the product and the response to the product cannot be ruled out’.

- Definitions for ‘Actual’ and ‘Potential’ medication errors; all (actual and potential) medication error reports would require 15-day expedited reporting.

- Nineteen medical conditions, which, if reported as AEs, would always be subject to 15-day expedited reporting, regardless of seriousness, outcome, or expectedness.
• 15-day expedited safety reporting requirements will be applied to human bioavailability and bioequivalence studies, whether or not conducted under an IND; additionally, any information that leads to a consideration of change in product administration or consideration of a change in the conduct of a study would also qualify for 15-day expedited reporting.

• A healthcare professional at the company will have to speak directly to the initial reporter of an ADR or medication error to obtain the information needed for a complete data set, i.e. letters will no longer be acceptable as a method of obtaining follow-up information; all active query efforts will have to be documented in detail in the report narrative.

• In addition to the usual 15-day follow-up reports, the sponsor will also have to submit a 30-day follow-up report to document specific efforts taken to obtain new information and the reason for the inability to obtain complete information if there is no new information.

• If the sponsor is unable to determine whether the outcome of an ADR was serious or non-serious, a report will need to be submitted to FDA in 45 days from time of first awareness with a detailed description of all active query attempts.

• Completion of all fields of the MedWatch Form 3500A will be required for US cases; completion of all fields on a CIOMS report will be required for cases of non-US origin.

• Use of the MedDRA dictionary will be required for coding ADRs in individual case safety reports.

• All licensing partners and others defined as ‘contractors’ would have to exchange all serious and non-serious ADRs and medication errors within five calendar days.

• US-specific implementation of ICH E2C periodic reporting standards. Although the framework for periodic reports will be based upon E2C, the proposal includes unique Interim Periodic Safety Reports (IPSRs) and semi-annual submission of individual case safety reports. It is also proposed that there are various US-specific addenda as a supplement to each PSUR. The schedule for submission of reports will be amended, although it will remain different to the schedule in operation in the EU and Japan. Retention of ‘traditional’ US periodic reports for legacy products will be allowed for those companies that wish to retain this system for the older products.

Japan

Legal basis and regulatory framework

The Pharmaceutical Affairs Law provides the legal basis for pharmacovigilance requirements in Japan, supplemented by a variety of communications issued by the MHLW.

The management of safety information obtained during clinical trials conducted in Japan

In response to health scares associated with HIV contamination of blood products used by haemophiliacs in the 1980s and, more recently, unexpected side effects from various drug products, there are a series of post-marketing provisions. The most important are provided by:

- Standard for implementation of post-marketing surveillance for the re-examination application of new drugs (1991)
- Standard for the conduct of good post-marketing surveillance practice (GPMSP) (1993) and MHLW Ordinance No. 10 (GPMSP) (1997)
- Ordinance No. 29 – Enforcement of the pharmaceutical affairs law, Article 66-7 (1997)

**General requirements**

All Japanese companies must make the following provisions for the conduct of PMS:

- establish ‘PMS Management Departments’ with sufficient qualified staff and independent of sales/marketing departments;
- appoint a ‘Responsible Person’ for PMS management;
- prepare and comply with relevant standard operating procedures.

**Definitions**

Japanese definitions are generally in accordance with those specified in ICH guidelines. The MHLW has utilized the ICH definition of a serious AE but without the inclusion of the ‘medically important’ criterion and ‘disability’ is defined as any disablement that is a permanent dysfunction such that it causes a disturbance in daily life; in practice, companies can operate successfully in Japan using the ICH definitions.

**Investigational products**

Japanese expedited reporting requirements for investigational products are generally consistent with the ICH E2A guideline. However, the requirements also specify that fatal or life-threatening expected ADRs qualify for 15-day reports (see Table 9.8). These requirements are regardless of the country of origin of the case report. The requirements also apply to the following:

- ADRs that relate to products marketed in Japan that are also subject to clinical investigation for new formulations or indications; such ADRs require duplicate reporting to the respective divisions within the MHLW that handle investigational and marketed products;
any reports of infection that occur in association with the administration of a parenteral drug product.

In addition, 15-day reports should be filed if results from clinical research indicate an increased frequency of ADRs, lack of efficacy or the possibility of an association with onset of cancer, important medical events, disability/incapacity, or a fatal outcome.

The MHLW has indicated that the sponsor should assess the causal relationship for all serious AEs that occur in clinical trials on products that are under clinical investigation in Japan, even if the AE occurs abroad. In addition, each report should include a formal assessment of the clinical importance of the case and relevant previous experience with the same or similar medicinal products.

There are no requirements in Japan for submission of periodic safety updates before marketing authorization is granted. However, as submissions in Japan often taken place once a product has been marketed elsewhere, it is usual for the Japanese NDA (‘Gaiyo’) submission to include a PSUR summarizing overseas post-marketing safety experience.

**Marketed products**

*Post-marketing surveillance activities*

Once a company secures approval to market a drug in Japan, it must evaluate the product’s safety over a 4, 6 or 10 year ‘re-examination’ period, dependent upon the nature of the drug.

The activities that must take place in the early post-marketing phase are as follows:

- early post-marketing phase vigilance (EPPV);
- Clinical Experience Investigation (CEI) studies;
- special studies and post-marketing clinical trials as instructed by the MHLW at the time of approval; these may include
  - drug utilization studies;
  - studies deemed necessary as a result of issues arising from pre-approval clinical trials, reports of ADRs, communicable diseases, etc.,
  - studies for identifying, validating or confirming information about the appropriate use of the product.

**Early post-marketing phase vigilance** Recent regulations require companies to conduct
EPPV during the first 6 months after launch of a new product on the Japanese market, the objectives being:

- to assure that appropriate information has been provided to prescribers;
- to encourage caution;
- to promote an understanding of appropriate use of the product in medical institutions;
- to report promptly spontaneous information on serious ADRs and infections and to implement the consequent safety measures and minimize the associated public health risk.

Clinical Experience Investigation studies

CEI studies are also a post-marketing requirement, their objectives being:

- to detect unlabelled ADRs;
- to understand ADR development during actual use of the drug;
- to define factors suspected to influence the product’s safety and/or efficacy profile.

In addition, for orphan drugs and others where required, CEI studies also have the purpose of characterizing efficacy and safety in actual drug usage conditions.

The number of cases to be studied is determined according to the characteristics of the drug.

Special studies and post-marketing clinical trials

Special studies include the following:

- studies on efficacy and safety in patients with special situations, e.g. children, elderly, pregnant women, and patients with renal or hepatic disease; conducted to refine or confirm associated prescribing information relating to ‘special’ patients that were not adequately investigated in pre-approval clinical studies.
- studies on long-term use.
- studies for the detection or confirmation of factors likely to affect efficacy and safety, e.g. the time to onset of ADRs.
- studies concentrating on the collection of information on AEs for which causality cannot be easily determined due to the small number of cases, to confirm or refute causality to the drug in question.

Post-marketing clinical trials may include:

- studies for establishing the most appropriate use in patients with special backgrounds, e.g. patients with renal disorders.
• studies based on pharmacoepidemiological methods for verifying prolongation of life from long-term use, improvement in quality of life, etc.

• studies for verifying efficacy and safety in accordance with the guidelines for the clinical evaluation of new drugs.

• studies for verification that factors identified as likely to affect efficacy or safety do so in practice.

**Expedited reports**

Expedited reporting requirements for marketed products depend on several factors, including the country of origin and the seriousness, severity and ‘expectedness’ of the ADR, as illustrated in Table 9.9.

<table>
<thead>
<tr>
<th>Report</th>
<th>Origin</th>
<th>ADRs that qualify for reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-day</td>
<td>Domestic</td>
<td>Serious unexpected(^a)</td>
</tr>
<tr>
<td></td>
<td>Foreign</td>
<td>Serious unexpected</td>
</tr>
<tr>
<td></td>
<td>Scientific literature</td>
<td>Serious</td>
</tr>
<tr>
<td>30-day</td>
<td>Domestic</td>
<td>Serious expected</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe/moderate non-serious</td>
</tr>
</tbody>
</table>

\(^a\) Fatal unexpected ADR: immediate preliminary notification to be followed by full written report.

Thirty-day reports should also be filed if results from clinical research indicate that a marketed product is associated with an increased frequency of ADRs, lack of efficacy or the possibility of an association with onset of cancer, important medical events, disability/incapacity, or a fatal outcome.

Although not explicitly stated in the legislation, common understanding is that the time frame for reporting begins from the date of receipt of information by the Japanese business/affiliate. All reports should be submitted on Japanese forms and in one of the Japanese languages.

A recent Notification (IYAKUAN No. 0531001) indicates that electronic reporting will be mandatory for post-marketing expedited reports with effect from 1 October 2003, with relevant data fields coded using MedDRA.

**Infections** The Pharmaceutical Affairs Law requires all domestic and foreign reports of fatal/life-threatening or other serious infections, associated with possible contamination of marketed drug products, to be notified immediately to the MHLW as preliminary reports by fax, with written reports within 15 days, whether labelled or not.

Domestic cases of moderate unexpected infection must be notified within 30 days.

**Measures taken abroad** In addition to the requirements that apply to individual ADR reports, companies should notify the MHLW on an expedited basis about any measures
taken abroad that relate to safety issues, e.g. addition of a new precautionary statement to a US product label. This applies equally to marketed products and those under clinical investigation in Japan.

**Periodic reports**

PSURs should be submitted to MHLW for all marketed products. These should be produced in full accordance with ICH E2C and include foreign data. Within (or attached to) each PSUR there should be a commentary on the safety information presented in the Japanese prescribing text(s) for the product.

In addition, periodic reports are required to summarize the progress of all Japanese post-marketing studies. Their content should include:

- the number of patients recruited, including the reason for any delay in the planned schedule for recruitment;
- comments on any factors derived from the statistical analysis that might influence the safety/efficacy profile of the product;
- a list of reported ADRs and/or infections, organized by body system;
- copies of ADR case reports previously sent to the MHLW;
- future measures to be taken as a result of the investigation.

Periodic safety updates (whether PSURs or post-marketing study updates) should be submitted every 6 months for 2 years following approval of the JNDA, and on an annual basis thereafter during the defined ‘re-examination’ period. Following completion of ‘re-examination’, the reports then revert to a 5 year periodicity.

The ‘clock’ may be reset to zero if the product has been approved for a new indication or formulation (depending on negotiation with the MHLW). Although the schedule for submission should be based on the date of marketing approval in Japan, the reporting period for each set of data may be determined from the IBD, in order to facilitate harmonization of Japanese PSURs with those produced elsewhere.

**Acknowledgements**

Wherever possible, the information provided within this chapter has been drawn from publicly available regulations and guidelines produced by CIOMS, ICH and regulatory authorities. On occasions, additional information has been included that was made available to the author through publications or symposia on ADR reporting, as well as personal communications with colleagues within AstraZeneca or other companies.

Indeed, I am indebted to my many colleagues in AstraZeneca who have provided the necessary information, and who have reviewed draft sections, for this chapter to be completed.
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