Guideline on Good Pharmacovigilance Practices

Module I- Management and reporting of adverse drug reactions

Turkish Medicines and Medical Devices Agency
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Chapter I
Purpose, Scope and Definitions

1.1 Purpose

This guideline sets forth the principles and particulars for implementing the Regulation on Drug Safety to assist marketing authorization holders in fulfilling their obligations as regards the systematic monitoring of adverse reactions, the collection, recording, assessment, and archiving of pertinent data, coordination of contact with all relevant parties, and the management and reporting of adverse reactions to ensure safe use of drugs.

1.2 Scope

This guideline addresses the legal requirements which are applicable to the Agency and marketing authorization holders as regards the collection, data management and reporting of suspected adverse reactions (serious and non-serious) associated with medicinal products authorized in Turkey. Aspects regarding the reporting of emerging safety issues or of suspected adverse reactions occurring in special situations are also presented in this guideline.

This guideline does not address the collection, management and reporting of events or patters of use, which do not result in suspected adverse reactions (e.g. asymptomatic overdose, abuse, off-label use, misuse or medication error) or which do not require to be reported as an individual case safety report (ICSR) or as an emerging safety issue. However, this information may need to be collected and presented in periodic safety update reports for the interpretation of safety data or for the benefit/risk evaluation of medicinal products.

1.3 Definitions

The definitions provided in the Regulation will apply for the purposes of this guideline, particularly with regard to the definitions provided in this section.

1.3.1 Adverse reaction

An adverse reaction is a response to a medicinal product which is noxious and unintended. This includes adverse reactions which arise from:

- the use of a medicinal product within the terms of the marketing authorization;
- the use outside the terms of the marketing authorization (i.e. overdose, off-label use, misuse, abuse and medical errors);
- occupational exposure.

1.3.2 Individual case safety report (ICSR)

This is an adverse drug reaction report, involving the reporting of one or several suspected adverse reactions in relation to a medicinal product that occur in a single patient at a specific point of time. A valid report should include at least one identifiable reporter, one single identifiable patient, at least one suspect adverse reaction and at least one suspect medicinal product.

1.3.3 Primary source

The primary source of the information on a suspected adverse reaction(s) is the person who reports the event. Several primary sources, such as healthcare professionals and/or a consumer, may provide information on the same case. In this situation, all the details regarding the primary sources should be included in the case report.

For the purposes of reporting suspect adverse reactions, a healthcare professional is a physician, pharmacist, dentist, nurse or midwife.

For the purposes of reporting suspect adverse reactions, a consumer is a person who is not a healthcare professional, such as a patient or a lawyer, a friend, or a relative/parent/child of a patient.

In the case of a consumer report, it is considered that a spontaneous report has been confirmed by a healthcare professional if medical documentations (e.g. laboratory or other test data) have been provided which support the occurrence of the suspected adverse reaction or which indicate that an identifiable healthcare professional suspected a reasonable possibility of causal relationship between a medicinal product and the reported adverse event.

If a consumer initially reports more than one reaction and at least one of these receives medical confirmation, the whole report should be documented as a spontaneous report confirmed by a healthcare professional and be reported accordingly. Similarly, if a report is submitted by a medically qualified patient, friend, relative of the patient or caregiver, the case should be also considered as a spontaneous report confirmed by a healthcare professional.

1.3.4 Serious adverse reaction

A serious adverse reaction is any adverse reaction that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, is a congenital anomaly/birth defect.

The characteristics/consequences should be considered as the time of the reaction to determine the seriousness of a case. For example, the term ‘life-threatening’ refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that could hypothetically cause death, had it been more severe.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered as serious reactions. Some medical events may jeopardize the patient or may require an intervention to prevent one of the above consequences. Such important medical events should be considered as ‘serious.’ Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Suspected transmission of an infectious agent should be also considered as a serious adverse reaction.

The important medical event (IME) terms list, developed by the EudraVigilance Expert Working Group based on the Medical Dictionary for Regulatory Activities (MedDRA) to facilitate the classification suspected adverse reactions, the analysis of aggregated data and the assessment of the ICSRs, will be subsequently posted on the Agency’s website for pharmacovigilance use in Turkey.

1.3.5 Overdose

This refers to the administration of a quantity of a medicinal product given per administration or cumulatively, which is above the maximum recommended dose according to the Agency-authorized summary of product characteristics. Clinical judgment should be always applied to establish overdosing.

1.3.6 Off-label use

The use of a medicinal product outside the indications and/or standard doses and/or the age range authorized in Turkey, and the importation of a medicinal product not yet authorized in Turkey for named patient use are considered as “off-label use.”

1.3.7 Medicinal product

A medicinal product is any substance or combination of substances, presented as having properties for diagnosing, treating or preventing disease in human beings, or which may be used in human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action.

This guideline applies to not only medicinal products authorized in Turkey, but also all medicinal products commercialized abroad by the same marketing authorization holder.

1.3.8 Abuse of medicinal products

This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

1.3.9 Occupational exposure

This refers to the exposure to a medicinal product as a result of one's professional or non-professional occupation.

1.3.10 Causality

The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterized by the fact that a casual relationship between a medicinal product and an occurrence is suspected. For the purposes of reporting to TÜFAM, if an event is spontaneously reported, even if the relationship is unknown or unstated, it meets the definition of an adverse reaction.

Therefore all spontaneous reported notified by healthcare professionals, patients or consumers are considered suspected adverse reactions, unless the reporter specifically states that they believe the events to be unrelated or that a casual relationship can be excluded.

1.3.11 Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorized product information.

Chapter II
Structures and Processes

2.1 Collection of reports

Two types of safety reports exists in the post-authorization phase: reports originating from unsolicited sources and reports originating from solicited sources.

Marketing authorization holders should take appropriate measures in order to collect and collate all reports of suspected adverse reactions originating from unsolicited or solicited sources. For this purpose, a pharmacovigilance system should be developed to allow the acquisition of sufficient information for the scientific evaluation of those reports. The system should be designed so that it helps to ensure that the collected reports are authentic, legible, accurate, consistent, verifiable and as complete as possible for their clinical assessment. The system should also be structured in a way that allows for reports of suspected adverse reactions to be validated in a timely manner and exchanged between the Agency and marketing authorization holders within the legal reporting timeframe.

2.1.1 Reports originating from unsolicited sources

2.1.1.1 Spontaneous reports

A spontaneous report is an unsolicited communication by a healthcare professional or consumer to the Agency or the marketing authorization holder that describes one or more suspected adverse reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection program.

Reports that follow a direct healthcare professional communication, publication in the press, questioning of healthcare professionals by company representatives, including product promotion representatives, communication from patients' organizations to their members, or class action lawsuits should be considered spontaneous reports.

Unsolicited consumer adverse reaction reports should be handled as spontaneous reports, irrespective of any subsequent 'medical confirmation.'

2.1.1.2 Literature reports

The scientific and medical literature is a significant source of information for the monitoring of the safety profile and of the risk-benefit balance of medicinal products, particularly in relation to the detection of new safety signals or emerging safety issues. Marketing authorization holders are therefore expected to maintain awareness of possible publications through a systematic literature review of widely used reference databases (e.g. Medline, Excerpta Medica or Embase) no less frequently than once a week. The marketing authorization holder should ensure that the literature review includes the use of reference databases that contain the largest reference of articles in relation to the medicinal product properties. In addition, marketing authorization holders should have procedures in place to monitor scientific and medical publications in local journals in countries where medicinal products have a marketing authorization, and to bring them to the attention of the company safety department as appropriate.

Reports of suspected adverse reactions from the scientific and medical literature, including relevant published abstracts from meetings and draft manuscripts, should be reviewed and assessed by marketing authorization holders to identify and record ICSRs originating from spontaneous reports or non-interventional post-authorization studies .

If multiple medicinal products are mentioned in the publication, only those which are identified by the publication's author(s) as having at least a possible causal relationship with the suspected adverse reaction should be considered by the concerned marketing authorization holder(s).

Valid ICSR's mentioning cases that have occurred in Turkey should be recorded according to the modalities detailed in 2.7 and 2.7.1.

One case should be created for each single identifiable patient. Relevant medical information should be provided and the publication author(s) should be considered as the primary source(s).

2.1.1.3 Reports from other sources

If a marketing authorization holder becomes aware of a report of suspected adverse reactions originating from a non-medical source (e.g. the press or other media), it should be handled as a spontaneous report. Every attempt should be made to follow-up the case to obtain the minimum information that constitutes a valid ICSR. The same reporting time frames should be applied as for other spontaneous reports.

2.1.1.4 Information on suspected adverse reactions from the Internet or digital media

Marketing authorization holders should regularly screen the Internet/digital media under their management or responsibility, such as web sites, web pages, blogs, vlogs, social networks, Internet forums, chat rooms, or health portals, for potential reports of suspected adverse reactions. In this aspect, digital media is considered to be company sponsored if it is owned, paid for and/or controlled by the marketing authorization holder. A donation (financial or otherwise) to an organization/site by a marketing authorization holder does not constitute ownership, provided that the marketing authorization holder does not control the final content of the site.

The frequency of the screening should allow for potential valid ICSRs to be reported to TÜFAM within the appropriate reporting timeframe based on the date the information was posted on the Internet site/digital medium.

Marketing authorization holders should also utilize their own websites to facilitate the collection of reports of suspected adverse reactions (see 3.1.1).

If a marketing authorization holder becomes aware of a report of suspected adverse reaction described in any non-company sponsored digital medium, it should assess the report to determine whether it qualifies for reporting.

Unsolicited cases of suspected adverse reactions from the Internet or digital media should be handled as spontaneous reports. The same reporting time frames as for spontaneous reports should be applied.

In relation to cases from the Internet or digital media, the identifiability of the reporter refers to the existence of a real person, that is, it is possible to verify the contact details of the reporter (e.g., an email address under a valid format has been provided).

2.1.2 Reports originating from solicited sources

Solicited reports of suspected adverse reactions are those derived from organized data collection systems, which include clinical trials, non-interventional studies, registries, off-label or named patient use, other patient support and disease management programs, surveys of patients or healthcare providers, compassionate use programs or information gathering on efficacy or patient compliance. Adverse reactions reports obtained from any of these data collection systems should not be considered spontaneous. This is with the exception of suspected adverse reactions originating from off-label use where adverse events are not actively sought. Reports from clinical trials should be conducted according to the “Regulation on Clinical Trials” and related guidelines.

For the purpose of this guideline, adverse reactions from name patient use, off-label use, patient support and disease management programs, and surveys of patients or healthcare providers are defined as reports from solicited sources.

Marketing authorization holders should conduct appropriate causal assessment and have in place a system to collect full and comprehensive case information and to evaluate that information in order to determine whether the collected adverse events are possibly related to the studied medicinal product and should be classified and processed as ICSRs of suspected adverse reactions. Only adverse reactions which are suspected to be related to the studied medicinal product by the primary source or the receiver of the case should be reported. They should be considered as solicited reports, and the report submitted to the Agency should highlight that the report is not spontaneous, and from a solicited source.

Adverse reactions from patient support programs frequently originate from telephone conversations that nurses responsible to conduct the program make with the patients. According to the agreement between the marketing authorization holder and the company responsible to conduct the program, all adverse events must be reported to the marketing authorization holder (e.g. intoxication from carbon monoxide released from a wood-burning stove, a surgical intervention while under the drug, to correct a pre-existing scar, etc.) Such adverse events should first be given consideration by the marketing authorization holder’s pharmacovigilance unit, and only those that qualify as a serious adverse reaction reported to TÜFAM. If the marketing authorization holder has hesitations regarding

this assessment, the physician concerned should be contacted to challenge causality, and only those that involve a suspected causal relationship with the product reported to TÜFAM.

There may be adverse reaction reports related to other medicinal products, other than the one involved in the patient support program. In those situations, if there is no interaction with the medicinal product being studied, the marketing authorization holder conducting the patient support program should forward these report to the marketing authorization holder of the suspect product, who should then report the same to TÜFAM according to the reporting requirements. When submitting the report to TÜFAM, it should be highlighted that the report originated from a patient support program conducted by another marketing authorization holder.

2.2 Validation of reports

Only valid ICSRs should be reported and all reports of suspected adverse reactions should be validated before reporting them to the Agency to make sure that the minimum criteria for reporting are included in the reports. The minimum criteria include the following:

- One identifiable reporter (primary source), characterized by professional qualification (e.g. physician, pharmacist, dentist, nurse, midwife, lawyer, consumer or other non-healthcare professional) name, initials or address. Whenever possible, contact details for the reporter should be recorded so that follow-up activities can be performed. However, if the reporter does not wish to provide contact details, the party receiving the report should confirm this with the reporter, and indicates it on the ICSR. All parties providing case information should be identifiable, not only the reporter.
- One single identifiable patient characterized by initials, file number, date of birth, age, age group or adress. The information should be as complete as possible.
- One or more suspected substance/medicinal product (the classification of medicinal products as suspect, interacting or concomitant should be based on the information provided by the primary source).
- One or more suspected adverse reaction.

If the primary source has made an explicit statement that a causal relationship between the medicinal product and the adverse event has been excluded and the receiver (the Agency or the marketing authorization holder) agrees with this, the report does not qualify as a valid ICSR since the minimum information is incomplete. The report does not also qualify as a valid ICSR if it is reported that the patient experienced an unspecified adverse reaction and there is no information provided on the type of adverse reaction experienced. Similarly, the report is not valid if only an outcome (or consequence) is notified and (i) no further information about the clinical circumstances is provided to consider it as a suspected adverse reaction, or (ii) the primary source has not indicated a possible causal relationship with the suspected medicinal product. For instance a marketing authorization holder is made aware that a patient was hospitalized or died, without any further information. In this particular situation, medical judgment should always be applied in deciding whether the notified information is an adverse reaction or an event. For example, a report of sudden death would usually need to be considered as a case of suspected adverse reaction and reported.

The lack of any of these four elements means that the case is considered incomplete and does not qualify for reporting. Marketing authorization holders are expected to exercise due diligence in following up the case to collect the missing data elements. Reports, for which the minimum information is incomplete, should nevertheless be recorded within the marketing authorization holder’s pharmacovigilance system for use in on-going safety evaluation activities.

When collecting reports of suspected adverse reactions via the Internet or digital media, the term ‘identifiable’ refers to the possibility of verification of the existence of a reporter and a patient.

When one party (the Agency or a marketing authorization holder) is made aware that the primary source may also have reported the suspected adverse reaction to another concerned party, all the relevant information necessary for the detection of the duplicate case should be included in the ICSR.

A valid case of suspected adverse reaction initially submitted by a consumer cannot be downgraded to a report of non-related adverse event if the contacted healthcare professional (nominated by the consumer for follow-up information) disagrees with the consumer’s suspicion. In this situation, the opinions of both the consumer and the healthcare professional should be included in the ICSR.

For solicited reports of suspected adverse reactions (see 2.1.2), where the receiver disagrees with the reasonable possibility of causal relationship between the suspected medicinal product and the adverse reaction expressed by the primary source, the case should not be downgraded to a ‘report of non-related adverse event.’ The opinions of both the primary source and the receiver should be recorded in the ICSR.

The same principle applies to the ICSR seriousness criterion, which should not be downgraded from ‘serious’ to ‘non-serious’ if the receiver disagrees with the seriousness reported by the primary source.

2.3 Follow-up of reports

When first received, the information in suspected adverse reactions reports may be incomplete. These reports should be followed-up as necessary to obtain supplementary detailed information significant for the scientific evaluation of the cases. This is particularly relevant for monitored events of special interest, prospective reports of pregnancy, cases notifying the death of a patient, cases reporting new risks or changes in the known risks. This is in addition to any effort to collect missing minimum information (see 2.2). Any attempt to obtain follow-up information should be documented.

Follow-up methods should be customized for the case to optimize the collection of missing information. This should be done in ways that encourage the primary source to submit relevant new information. Requesting the primary source to repeat information already provided in the initial report and/or to complete extensive questionnaires should be avoided, as this may discourage future spontaneous reporting by this source. Therefore, consideration should be given to pre-populating some data fields in those follow-up report forms to make their completion by the primary source more convenient.

If the information received directly from a consumer is incomplete but suggests that an adverse reaction may have occurred, attempts should be made to obtain consent to contact a nominated healthcare professional to obtain further follow-up information. When such a case, initially reported by a consumer, has been confirmed (totally or partially) by a healthcare professional, this information should be clearly highlighted in the ICSR.

For suspected adverse reactions relating to biological medicinal products, the definite identification of the concerned product with regard to its manufacturing is of particular importance. Therefore, all appropriate measures should be taken to clearly identify the name of the product and the batch number.

2.4 Data management

Electronic data and paper reports of suspected adverse reactions should be stored and treated in the same way as other medical records with appropriate respect for confidentiality rules regarding patients' and reporters' identifiability. Confidentiality of patients' records including personal identifiers (if provided) should always be maintained. Identifiable personal details of reporting healthcare professionals should be kept in confidence. However, if this information is included in the reports that the marketing authorization holder will be making to TÜFAM, the reporter's identifiable personal details and contact details should be submitted. With regards to patient's and reporter's identifiability, transmission of case report information from TÜFAM to the marketing authorization holder should respect the confidentiality rules.

In order to ensure pharmacovigilance data security and confidentiality, strict access controls should be applied to documents and to databases to authorized personnel only.

Data received from the primary source should be treated in an unbiased and unfiltered way and inferences as well as attributions should be avoided during data entry or electronic transmission. The reports should include the verbatim text as used by the primary source. The original verbatim text should be coded using the appropriate terminology.

Electronic data storage should allow traceability of all data entered or modified, including dates and sources of received data, as well as dates and destinations of transmitted data.

A procedure should be in place to account for identification and management of duplicate cases at data entry and during the generation of aggregated reports.

2.5 Quality management

Marketing authorization holders should have a quality management system in place to ensure compliance with the necessary quality standards at every stage of case documentation, i.e. data collection, data transfer, data management, data coding, case validation, case evaluation, case follow-up, ICSR reporting and case archiving. Conformity of stored data with initial and follow-up reports should be verified by quality control procedures, which permit for the validation against the original data. In this aspect, the source data (e.g., letters, emails, records of telephone calls) should be easily accessible.

Written standard operating procedures should guarantee that the roles and responsibilities and the required tasks are clear to all parties involved and that there is provision for proper control and, when needed, change of the system. This is equally applicable to activities that are contracted out to third parties, whose procedures should be reviewed to verify that they are adequate and compliant with applicable requirements.

Staff directly performing pharmacovigilance activities should be appropriately trained in applicable pharmacovigilance legislation and guidelines in addition to specific training in report processing activities for which they are responsible and/or undertake. Other personnel who may receive or process safety reports (e.g. clinical development, sales, medical information, legal, quality control) should be trained in adverse event collection and reporting in accordance with internal policies and procedures.

2.6 Special situations

2.6.1 Use of a medicinal product during pregnancy or breastfeeding

2.6.1.1 Pregnancy

Reports, where the embryo or fetus may have been exposed to medicinal products (either through maternal exposure or transmission of a medicinal product via semen following paternal exposure), should be followed-up in order to collect information on the outcome of the pregnancy and development of the child after birth. The recommendations provided in the 'Guideline on the Exposure to Medicinal Products during Pregnancy: Need for Post-Authorization Data,' which will be issued in the future, should be considered as regard the monitoring, collection and reporting of information in these specific situations in order to facilitate the scientific evaluation. When an active substance or one

of its metabolites has a long half-life, this should be taken into account when assessing the possibility of exposure of the embryo, if the medicinal product was taken before conception.

When pregnant women or healthcare professionals contact marketing authorization holders to request information on the teratogenicity of a medicinal product or experience of use during pregnancy, reasonable attempts should be made to obtain information on any possible medicinal product exposure to the embryo or fetus and to follow-up on the outcome of the pregnancy.

Reports of exposure to medicinal products during pregnancy should contain as many detailed elements as possible in order to assess the causal relationships between any reported adverse events and the exposure to the suspected medicinal product. In this context the use of standard structured questionnaires is recommended.

Individual cases with an abnormal outcome associated with a medicinal product following exposure during pregnancy are classified as serious reports and should be reported, in accordance with the requirements outlined in 2.7.

This especially refers to:

- reports of congenital anomalies or developmental delay, in the fetus or the child;
- reports of fetal death and spontaneous abortion; and
- reports of suspected adverse reactions in the neonate that are classified as serious.

Reports of induced termination of pregnancy without information on congenital malformation, reports of pregnancy exposure without outcome data or reports which have a normal outcome should not be reported since there is no suspected adverse reaction. These reports should however be collected and discussed in the periodic safety update reports.

However, in certain circumstances, reports of pregnancy exposure with no suspected reactions may need to be reported. This may be a condition of the marketing authorization or stipulated in the risk management plan. Examples include pregnancy exposure to medicinal products contraindicated in pregnancy, or medicinal products with a special need for surveillance because of a high teratogenic potential (e.g. thalidomide, isotretinoin).

A signal of a possible teratogenic effect (e.g. a cluster of similar abnormal outcomes) should be notified immediately to the Agency in accordance with the recommendations presented in 3.1.5.

2.6.1.2 Breastfeeding

Suspected adverse reactions which occur in infants following exposure to a medicinal product from breast milk should be reported to the Agency in accordance with the criteria outlined in 2.7.

2.6.2 Use of a medicinal product in the pediatric or elderly population

The collection of safety information in the pediatric or elderly population is important. Reasonable attempts should therefore be made to obtain and report the age or age group of the patient when a case is reported by a healthcare professional, or consumer in order to be able to identify potential safety signals specific to a particular population. As regards the pediatric population, the ‘Guideline on conduct of pharmacovigilance for medicines used by the pediatric population,’ to be published in the future, on the conduct of pharmacovigilance in this population should be followed.

2.6.3 Reports of overdose, abuse, off-label use, misuse, medical error or occupation exposure

Medication error refers to any unintentional error in the prescribing, dispensing, or administration of a medicinal product.

Reports of overdose, abuse, off-label use, misuse, medication error or occupational exposure with no associated adverse reaction should not be reported as ICSRs. They should be considered in periodic safety update reports as applicable. When those reports constitute safety issues impacting on the risk-benefit balance of the medicinal product, they should be notified to the Agency in accordance with the recommendations provided in 3.1.5.

Reports associated with suspected adverse reactions should be followed-up to ensure that the information is as complete as possible with regards to the symptoms, treatments, outcomes, context of occurrence (e.g., error in prescription, administration, dispensing, dosage, unauthorized indication or population, etc.).

2.6.4 Lack of therapeutic efficacy

Reports of lack of therapeutic efficacy should be recorded, followed-up if data is incomplete, and reported to the Agency within a 15-day time frame. Special care should be taken with reports involving medicinal products used in critical conditions or for the treatment of life-threatening diseases, vaccines, contraceptives are examples of such cases. This applies unless the reporter has specifically stated that the outcome was due to disease progression and was not related to the medicinal product.

Clinical judgment should be used when considering if a case of lack of therapeutic efficacy qualify for reporting. For example, an antibiotic used in a life-threatening situation where the medicinal product was not in fact appropriate for the infective agent should not be reported.

However, a life-threatening infection, where the lack of therapeutic efficacy appears to be due to the development of a newly resistant strain of a bacterium previously regarded as susceptible, should be reported within 15 days.

For vaccines, cases of lack of therapeutic efficacy should be reported, in particular with regard to potential signals of reduced immunogenicity in a sub-group of vaccinees, waning immunity, or strain replacement. With regard to the latter, it is considered that spontaneously reported cases of lack of therapeutic efficacy by a healthcare professional may constitute a signal of strain replacement. Such a signal may need prompt action and further investigation through post-authorization safety studies as appropriate.

2.7 Reporting of ICSR's

Only valid ICSRs (see 2.2) should be reported. The clock for the reporting of a valid ICSR starts as soon as the information containing the minimum reporting criteria has been brought to the attention of the Agency or of any personnel of the marketing authorization holder, including product promotion representatives and Contract Pharmacovigilance Service Providers (CPSPs). This date should be considered as day zero. In practice this is the first business day the receiver becomes aware of the information.

Where the marketing authorization holder has executed a contract with a person or an organization, explicit procedures and detailed agreements should exist between the parties to ensure that the marketing authorization holder can comply with the reporting obligations. These procedures should in particular specify the processes for exchange of safety information, including timelines and regulatory reporting responsibilities and should avoid duplicate reporting to the Agency.

For ICSRs described in the scientific and medical literature, the clock starts (day zero) with awareness of a publication containing the minimum information for reporting. Where a contract is executed with an organization to perform literature searches and/or report valid ICSRs (Any organization with searching capabilities may be acceptable if only searching is delegated. A CPSP is required if both searching and ICSR preparation are delegated), detailed agreements should exist to ensure that the marketing authorization holder can comply with the reporting obligations.

When additional significant information is received for a previously reported case, the reporting time clock starts again for the submission of a follow-up report from the date of receipt of the relevant follow-up information. For the purpose of reporting, significant follow-up information corresponds to new medical or administrative information that could impact on the assessment or management of a case or could change its seriousness criteria; non-significant information includes updated comments on the case assessment or corrections of typographical errors in the previous case version. See also 4.4 for the distinction between significant and non-significant follow-up information.

2.7.1 Reporting timeframes

In general, the reporting of serious valid ICSRs is required as soon as possible, but in no case later than 15 calendar days after initial receipt of the information by any personnel of the marketing authorization holder, including product promotion representatives, CPSPs or other contractors. This applies to initial and follow-up information. Where a case initially reported as 'serious' becomes 'non-serious,' based on new follow-up information, this information should still be reported within 15 days.

Chapter III
Responsibilities of marketing authorization holders

3.1 Responsibilities of marketing authorization holders

Each marketing authorization holder should have in place a system for the collection and recording of all reports of adverse reactions which are brought to its attention, whether reported spontaneously by healthcare professionals or consumers or occurring in the context of a post-authorization study.

Marketing authorization holders should establish mechanisms enabling the traceability and follow-up of adverse reaction reports while protecting the confidentiality of the data. Pharmacovigilance data and documents relating to individual authorized medicinal products should be retained for at least 10 years after the marketing authorization has expired.

In addition to the requirements laid down in this Chapter, the general principles detailed in Chapter II should be applied by marketing authorization holders to all reports of suspected adverse reactions.

3.1.1 Spontaneous reports

Marketing authorization holders will record all reports of suspected adverse reactions originating from within Turkey, which are brought to their attention spontaneously by healthcare professionals, or consumers. This includes reports of suspected adverse reactions received electronically or by any other appropriate means. In this context, marketing authorization holders should utilize their websites to facilitate the collection of reports of suspected adverse reactions by providing adverse reactions forms for reporting, or appropriate contact details.

3.1.2 Case reports published in the scientific and medical literature

General principles in relation to the monitoring for individual cases of suspected adverse reactions described in the scientific and medical literature are provided in 2.1.1.2. The requirements provided in this guideline for screening of the scientific and medical literature are part of the wider literature searches which need to be conducted for periodic risk/benefit assessment reports.

Marketing authorization holders should monitor all the active substances for which they hold a marketing authorization by accessing a widely used systematic literature review and reference database, in line with the principles detailed in 2.1.1.2 and Appendix 3.

Articles can be excluded from the reporting by the marketing authorization holder if another company's medicinal product is the suspected medicinal product. If a product name is not specified in the publication, all marketing authorization holders of medicinal products containing the active substance concerned must submit a report to TÜFAM.

If a literature article which presents data analyses from publicly available databases or which summarizes results from post-authorization studies suggests the existence of a new safety consideration that may impact on a medicinal product's risk-benefit profile, this should be immediately reported to the Agency, and discussed and analyzed in the relevant sections of the concerned periodic risk/benefit assessment report to the extent it affects the medicinal product's risk/benefit profile.

3.1.3 Suspected adverse reactions related to quality defects or counterfeit medicinal products

When a suspected adverse reaction is associated with a suspected or confirmed counterfeit medicinal product or quality defect of a medicinal product, an ICSR should be reported. The seriousness of the ICSR is linked to the seriousness of the reported suspected adverse reactions in accordance with the definitions provided in 1.3.4.

In order to protect public health, it may become necessary to implement urgent measures such as the recall of one or more defective batches of a medicinal product from the market. Therefore, marketing authorization holders should have a system in place to ensure that reports of suspected adverse reactions related to counterfeit medicinal products or to quality defects of a medicinal products are investigated in a timely fashion and that confirmed quality defects are notified separately to the manufacturer and to the Agency.

3.1.4 Suspected transmission of an infectious agent via a medicinal product

Any suspected transmission of an infectious agent via a medicinal product should be considered as a serious adverse reaction and such cases should be reported within 15 days. If no other criterion is applicable, the seriousness of this ICSR should be considered as an important medical event (see 1.3.4). This also applies to vaccines.

Marketing authorization holders should therefore have in place a system to inform consumers, Public Health Agency and Turkish Medicines and Medical Devices Agency of any transmission of an infectious agent via a medicinal product.

Any organism, virus or infectious particle (e.g. prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent.

A transmission of an infectious agent may be suspected from clinical signs or symptoms, or laboratory findings indicating an infection in a patient exposed to a medicinal product.

Emphasis should be on the detection of infections/infectious agents known to be potentially transmitted via a medicinal product, but the occurrence of unknown agents should also always be considered.

In the context of evaluating a suspected transmission of an infectious agent via a medicinal product, care should be taken to discriminate, whenever possible, between the cause (e.g., injection/ administration) and the source (e.g., contamination) of the infection and the clinical conditions of the patient at the time of the infection (immunosuppressed /vaccinee).

Confirmation of contamination (including inadequate inactivation/attenuation of infectious agents as active substances) of the concerned medicinal product increases the evidence for transmission of an infectious agent and may therefore be suggestive of a quality defect for which the procedures detailed in 3.1.3 should be applied.

Recommendations provided in the Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products should be followed.

3.1.5 Emerging safety issues

If suspected adverse reactions reported in a single ICSR affect the risk-benefit balance of the medicinal product, this should be considered as a "Emerging Safety Issue" and notified so to the Agency in writing, in addition to the reporting requirements. The points of concern and the actions proposed should be indicated on the cover page of the ICSR.

Events may occur, which do not fall within the definition of reportable valid ICSRs, and thus are not subject to the reporting requirements, even though they may lead to changes in the known risk-benefit balance of a medicinal product and/or impact on public health. Examples include:

- major safety findings from a newly completed non-clinical study;
- major safety concerns identified in the course of a non-interventional post-authorization study or of a clinical trial;
- signal of a possible teratogenic effect or of significant hazard to public health;
- safety issues published in the scientific and medical literature;
- safety issues arising from the signal detection activity or emerging from a new ICSR and which impact on the risk-benefit balance of the medicinal product and/or have implications for public health;
- safety issues related to the use outside the terms of the marketing authorization;
- safety issues due to misinformation in the product information (SmPC/PL);
- marketing authorization withdrawal, non-renewal, revocation or suspension outside Turkey for safety-related reasons;
- urgent safety restrictions outside Turkey;
- safety issues in relation to the supply of raw material;
  lack of supply of medicines.

These events/observations, which may affect the risk-benefit balance of a medicinal product, should be notified as "Emerging Safety Issues" to the Agency, both in writing and via e-mail. The document should indicate the points of concern and the actions proposed in relation to the marketing application/authorization for the concerned medicinal product. Those safety issues should also be analyzed in the relevant sections of the periodic benefit/risk assessment report of the authorized medicinal product.

3.1.6 Period between the submission of the marketing authorization application and the granting of the marketing authorization

In the period between the submission of the marketing authorization application and the granting of the marketing authorization, it is the responsibility of the applicant to ensure that information (quality, non-clinical, clinical) that could impact on the risk-benefit balance of the medicinal product under evaluation is immediately submitted to the Agency.

3.1.7 Period after suspension, revocation or withdrawal of marketing authorization

The marketing authorization holder will continue to collect any reports of suspected adverse reactions related to the concerned medicinal product following the suspension of a marketing authorization, and all the reporting requirements will remain in place. Where a marketing authorization is withdrawn or revoked, the former marketing authorization holder should continue to collect spontaneous reports of suspected adverse reactions originating within Turkey to, for example, facilitate the review of delayed onset adverse reactions or of retrospectively notified cases.

3.1.8 Reports from class action lawsuits

Reports arising from class action lawsuits should be managed as spontaneous reports. Valid ICSRs should describe the concerned adverse reactions. They should be reported in accordance with the timeframes and modalities described in 2.7 and 2.7.1.

Where large batches of potential ICSRs are received, marketing authorization holders may make a request to TÜFAM, in exceptional circumstances, for an exemption in order to submit serious cases of suspected adverse reactions within 30 days from their date of receipt instead of 15 days.

3.1.9 Reports from patient support programs and market research programs

A patient support program is an organized system where a marketing authorization holder receives and collects information relating to the use of a medicinal product.

A market research program refers to the systematic collection, recording and analysis by a marketing authorization holder of data and findings, relevant for marketing and business development.

Safety reports originating from those programs should be considered as solicited reports. Marketing authorization holders should have the same mechanisms in place as for all other solicited reports to manage that information and report cases of suspected adverse reactions.

Chapter IV
Preparation of Individual Case Safety Reports

4.1 Suspected adverse reactions

Diagnoses and provisional diagnoses, along with adverse reactions/events, symptoms, laboratory findings and the symptoms should be coded in line with the latest version of the MedDRA terminology (lowest level term).

The cover page provided in Appendix 1 should be used for reporting ICSRs.

If a diagnosis is reported with characteristic signs and symptoms, the proper handling will be to select a term for the diagnosis and to MedDRA code it in the section for suspected adverse reactions. However, signs and symptoms should be also specified in the case narrative section verbatim as reported by the initial reporter.

If no diagnosis is provided, all reported signs and symptoms should be listed and MedDRA coded in the section for suspected adverse reactions. If these signs and symptoms are typically part of a diagnosis, the diagnosis can be MedDRA coded in addition and included in the ICSR, specifically indicating ‘Sender's diagnosis/syndrome and/or reclassification of reaction/event.’

If other events have been reported, which are not typically signs or symptoms of the primary source's diagnosis or provisional diagnosis, and those events are suspected to be adverse reactions, they should also be listed and MedDRA coded in the section for ‘Suspected Adverse Reactions.’

In case the marketing authorization holder disagrees with the diagnosis reported by the primary source, an alternative diagnosis can be provided and included in the ICSR as ‘Sender's diagnosis/syndrome and/or reclassification of reaction/event’ in addition to the reported diagnosis provided in the section for ‘Suspected Adverse Reactions.’ In this situation, the marketing authorization holders should provide a reasoning for reclassifying the adverse reaction.

In the event of death of the patient, the date, cause of death including autopsy-determined causes should be provided as far as possible. If the death is unrelated to the reported suspected adverse reactions and is linked for example to disease progression, the seriousness criterion of the ICSR should not be considered as fatal.

4.2 Case narrative, causality assessment and comments

A case narrative should be provided, where possible ('where possible' should be interpreted as having received sufficient information from the primary source to prepare a concise clinical summary of the individual case), for all cases with the exception of non-serious cases. The information should be presented in a logical time sequence, in the chronology of the clinical course, therapeutic measures, outcome and follow-up information obtained. Any relevant autopsy or post-mortem findings should also be summarized.

The narrative should serve as a comprehensive, stand-alone 'medical report' containing all known relevant clinical and related information, including patient characteristics, therapy details, medical history, clinical course of the events, diagnosis, adverse reactions and their outcomes, relevant laboratory evidence (including normal ranges) and any other information that supports or refutes the suspected adverse reactions. An example of a standard narrative template is available in the Report of the CIOMS Working Group V.

The information provided in the narrative should be consistent with the data appropriately reflected in all the other relevant sections of the ICSR.

Where available, comments from the primary source on the diagnosis, causality assessment or other relevant issue, should be provided included in the ICSR as the 'Reporter's comments.' Marketing authorization holders may describe a disagreement with, and/or alternatives to the diagnoses given by the primary source (See 4.1). This should be included as the marketing authorization holder's comments, where discrepancies or confusions in the information notified by the primary source may also be highlighted. A summary of the points of concerns and actions proposed should also be included, if the ICSR leads to notification of an Emerging Safety Issue (3.1.5).

4.3 Test Results

Results of tests and procedures relevant to the examination of the patient should be provided. Results of tests and procedures relevant to the investigation of the patient should capture the tests and procedures performed to diagnose or confirm the reaction/event, including those tests done to investigate a non-drug cause, (e.g. serologic tests for infectious hepatitis in suspected drug-induced hepatitis). Both positive and negative results should be reported.

The coding of tests should be performed in line with MedDRA. If it is not possible to provide information on tests and test results in a structured manner, this information can be provided as free text.

4.4 Follow-up reports

Marketing authorization holders will report follow-up information when this becomes available. When submitting ICSRs to the Agency which have been updated with follow-up information, a separate text should be provided highlighting which information has been changed since the initial report in a logical chronological order.

In contrast, a follow-up report which contains non-significant information does not require to be reported. This may refer, for example, to minor changes to some dates in the case with no implication for the evaluation or transmission of the case, or corrections of typographical errors in the previous case version.

Medical judgment should be applied since a change to the birth date may constitute a significant modification (ör. if inconsistent with the age information of the patient).

Similarly, coding changes due to a version change of MedDRA (a valid term becoming invalid), can be considered as a non-significant change as long as this change has no impact on the medical content of a case. However, an amendment of the MedDRA coding due to a change in the interpretation of a previously reported suspected adverse reaction may constitute a significant change and therefore should be reported.

4.5 Special situations

4.5.1 Use of a medicinal product during pregnancy or breastfeeding

With regard to the electronic reporting of parent-child/fetus cases, the following should be adhered to:

In the situation where a fetus or nursing neonate is exposed to one or several medicinal products through the parent and experiences one or more suspected adverse reactions (other than early spontaneous abortion/fetal demise), information on both the parent and the child/fetus should be provided in the same report. These cases are referred to as parent-child/fetus reports. The information provided in the section 'Patients characteristics' applies only to the child/fetus. Characteristics of the parent (mother or father) who is the source of additional exposure to the medicinal product should be described in the section 'Relevant medical history.'

If both the parent and the child/fetus experience suspected adverse reactions, two separate reports, i.e. one for the parent (mother or father) and one for the child/fetus, should be created but they should be cross-referenced.

If there has been no reaction affecting the child, the parent-child/fetus report is not required. However, the relevant medical history section of the report prepared for the parent should include pregnancy and exposure information.

For those cases describing miscarriage or early spontaneous abortion, only a maternal report is required. However, if the suspect medicinal product was taken by the father, the relevant medical history section should specify that the medication was taken by the father.

4.5.2 Suspected adverse reaction reports published in the scientific and medical literature

The cover page provided in Appendix 2 should be used for reporting ICSR's published in the scientific and medical literature.

The literature references should be included in the cover page, in line with the Vancouver Convention (known as "Vancouver Style"), developed by the International Committee of Medical Journal Editors. The standard format as well as those for special situations can be found in the following reference: International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. N Engl J Med. 1997; 336: 309-15 (The Vancouver recommendations are also available on the International Committee of Medical Journal Editors website http://www.icmje.org).

In addition to the cover page, the full text of the article, a comprehendible Turkish abstract of the article, and the ICSRs for the cases referenced in the article should be submitted. A separate ICSR should be prepared for each case covered in the article; each of them should be assigned a unique case reference number; but all of them should be provided in a single submission to TÜFAM, attached with the article to which they belong. Adverse reactions, diseases and test results should be MedDRA coded in the ICSR.

If the same marketing authorization holder has multiple medicinal products containing the same active substance, it is sufficient to make a single submission by referencing each of those medicinal products in the cover page.

4.5.3 Suspected adverse reactions related to overdose, abuse, off-label use, misuse, medication error or occupation exposure

If a case of overdose, abuse, off-label use, misuse, medication error or occupational exposure is reported with clinical consequences, the MedDRA (Lowest Level Term) code, corresponding to the term closest to the description of the reported overdose, abuse, off-label use, misuse, medication error or occupational exposure should be selected.

4.5.4 Lack of therapeutic efficacy

If the primary source suspects a lack of therapeutic efficacy, the MedDRA (Lowest Level Term) code, corresponding to the term closest to the description of the reported lack of therapeutic efficacy, should be selected.

4.5.5 Suspected adverse reactions related to the quality defect or counterfeit medicinal products

In order to be able to clearly identify cases related to quality defect or counterfeit medicinal products, the following recommendations should be applied:

4.5.5.1 Quality defect

Where a report of suspected adverse reactions is associated with a suspected or confirmed quality defect of a medicinal product, the MedDRA (Lowest Level Term) code of the term corresponding most closely to the product quality issue should be added to the section for suspected adverse reactions.

4.5.5.2 Counterfeit medicinal products

Where a report of suspected adverse reactions is associated with a suspected or confirmed counterfeit ingredient, active substance or medicinal product, the MedDRA (Lowest Level Term) code of the term corresponding most closely to the reported information should be added to the suspected adverse reactions.

4.5.6 Suspected transmission of an infectious agent via a medicinal product

Suspicion of transmission of an infectious agent via a medicinal product should be coded using the MedDRA terminology (Lowest Level Term). In addition, if the infectious agent is specified, the MedDRA (Lowest Level Term) code corresponding most closely to the infectious agent should also be included in the section for suspected adverse reactions.

4.5.7 Reports originating from organized data collection systems and other systems

The following reporting rules should be applied based on (i) the type of data collection system and (ii) whether the suspected medicinal product is part of the scope of the data collection system:

1. For all patient support programs and named patient use programs where adverse events are actively sought:
    a. Where the adverse reaction is suspected to be related at least to the studied (or supplied) medicinal product:
        i. the report should be considered as solicited;
        ii. the ‘report type’ should be specified as ‘a report from a patient support program or named patient use.’
    b. Where the adverse reaction is only suspected to be related to a medicinal product which is not subject to the scope of the organized data collection system and there is no interaction with the studied (or supplied) medicinal product:
        i. the report should be considered as spontaneous report, since it conveys the suspicion of the initial reporter.
2. For named patient use where adverse event reporting is not actively sought:
    a. the report should be considered as spontaneous report, since it conveys the suspicion of the initial reporter.
3. All reports related to investigational medicinal products, comparators and/or rescue medications or concomitant medications must be submitted in line with the applicable guidelines, as provided in the Regulation on Clinical Trials.

All adverse reaction reports occurring during an observational studies should be managed in line with the Guideline for Observational Studies with Drugs.

Appendix 1 – Cover page for reporting adverse reactions

Turkish Ministry of Health — Date
Turkish Medicines and Medical Devices Agency — Number
Risk Management Office
Turkish Pharmacovigilance Center
Ankara

Subject: Adverse reaction report #..... for the medicinal product …….
Reference: (Specify the date, reference number and e-tracking number of any previous report-related correspondence with the Ministry)

Type of adverse reaction report:	Initial [ ] Follow-up [ ], with initial report date and e-tracking number:
Case reference number:	
Suspected drug(s):	
Adverse reaction(s):	
Is the adverse reaction specified in the SmPC?	Yes [ ] No [ ]
Causality assessment / marketing authorization holder's comments:	

I do hereby warrant that the documents submitted to TİTCK are identical to the ones uploaded to the system.

Signature
Qualified Person / Deputy Qualified Person Responsible for Pharmacovigilance

Appendix 2 – Cover page for reporting literature

Turkish Ministry of Health — Date
Turkish Medicines and Medical Devices Agency — Number
Risk Management Office
Turkish Pharmacovigilance Center
Ankara

Subject: Literature report regarding the product ……..

LITERATURE Described according to the Vancouver Style reference guideline.	
Type of report:	Initial [ ] Follow-up [ ], with initial report date and e-tracking number:
Case reference number:	
Name(s), ATC code(s) and active substance(s) of the suspected medicinal product(s):	
Adverse Reaction(s):	Number of cases:
Is the adverse reaction specified in the SmPC?	Yes [ ] No [ ]

I do hereby warrant that the documents submitted to TİTCK are identical to the ones uploaded to the system.

Signature
Qualified Person / Deputy Qualified Person Responsible for Pharmacovigilance

Appendix 3 – Detailed guidance on the monitoring of scientific and medical literature

Appendix 3.1 When to start and stop searching in the scientific and medical literature

In addition to the reporting of serious ICSRs or presentation of serious and non-serious ICSRs in periodic benefit/risk assessment reports, the marketing authorization holder has an obligation to review the worldwide experience with medicinal product in the period between the submission of the marketing authorization application and the granting of the marketing authorization. The worldwide experience includes published scientific and medical literature. For the period between submission and granting of a marketing authorization, literature searching should be conducted to identify published articles that provide information that could impact on the risk-benefit assessment of the product under evaluation. For the purpose of the preparation of periodic benefit/risk assessment reports and the notification of emerging safety issues, the requirement for literature searching is not dependent on a product being marketed. Literature searches should be conducted for all products with a marketing authorization, irrespective of commercial status. It would therefore be expected that literature searching would start on submission of a marketing authorization application and continue while the authorization is active.

Appendix 3.2 Where to look

Articles relevant to the safety of medicinal products are usually published in well-recognized scientific and medical journals, however, new and important information may be first presented at international symposia or in local journals. Although the most well-known databases (e.g. Medline) cover the majority of scientific and medical journals, the most relevant publications may be collated elsewhere. A marketing authorization holder should therefore establish the most relevant source of published literature for each product.

Medline, Embase and Excerpta Medica are often used for the purpose of identifying ICSRs. These databases have broad medical subject coverage. The database providers can advise on the sources of records, the currency of the data, and the nature of database inclusions. It is best practice to have selected one or more databases appropriate to a specific product. For example, in risk-benefit assessment, safety issues arising during non-clinical safety studies may necessitate regular review of a database that has a less clinical focus and includes more laboratory-based publications.

Relevant published abstracts from meetings and draft manuscripts should be reviewed for reportable ICSRs and for inclusion in periodic benefit/risk assessment reports. Although it is not a requirement for marketing authorization holders to attend all such meetings, if there are company personnel at such a meeting, or it is sponsored by a marketing authorization holder, it is expected that articles of relevance would be available to the marketing authorization holder's pharmacovigilance system. In addition, literature that is produced or sponsored by a marketing authorization holder should be reviewed, so that any reportable ICSRs can be reported to TÜFAM as required in advance of publication. If ICSRs are brought to the attention of a marketing authorization holder from this source, they should be processed in the same way as ICSRs found on searching a database or reviewing a journal.

Abstracts from major scientific meetings are available in some databases, but posters and communications are rarely available from this source.

Appendix 3.3 Database searches

A search is more than a collection of terms used to query a database. Decisions about the database selection, approach to records retrieval, term or text selection and the application of limits need to be relevant to the purpose of the search. For searches in pharmacovigilance, some of the considerations for database searching are described below.

Appendix 3.3.1Precision and recall

Medical and scientific databases are a collection of records relating to a set of publications. For any given record, each database has a structure that facilitates the organization of records and searching by various means, from simple text to complex indexing terms with associated subheadings. Search terms (text or indexed) can be linked using Boolean operators and proximity codes to combine concepts, increasing or decreasing the specificity of a search. In addition, limits to the output can be set. When searching, the application of search terms means that the output is less than the entire database of the records held. The success of a search can be measured according to precision and recall (also called sensitivity). Recall is the proportion of records retrieved ("hits") when considering the total number of relevant records that are present in the database. Precision (sensitivity) is the proportion of "hits" that are relevant when considering the number of records that were retrieved. In general, the higher recall searches would result in low precision (sensitivity).

Appendix 3.3.2Search construction

Databases vary in structure, lag time in indexing and indexing policy for new terms. While some database providers give information about the history of a particular indexing term or the application of synonyms, other databases are less sophisticated. In addition, abstracts are not always consistent in the choice of words relating to pharmacovigilance concepts or medicinal products/active substances names.

When performing a search for pharmacovigilance, the highest recall for a search would be to enter the medicinal product name and active substance name (in all their variants) only. In practice, additional indexing terms and text are added to increase precision and to reduce the search result to return records that are of relevance to pharmacovigilance. There is a balance to be achieved. It is, therefore, expected that complicated searches are accompanied by initial testing to check that relevant records are not omitted, however, there is no defined acceptable loss of recall when searching for pharmacovigilance purposes. Term selection should be relevant to the database used and the subject of the search.

Appendix 3.3.3Selection of product terms

Searches should be performed to find records for active substances and not for brand names only. This can also include excipients or adjuvants that may have a pharmacological effect. When choosing search terms for medicinal products, there are a number of considerations.

- Is the active substance an indexed term?
- What spellings might be used by authors (particularly if the active substance is not indexed)?
- What alternative names might apply (chemical names, brand names, active metabolites)?
- Is it medically relevant to search only for a particular salt or specific compound for an active substance?

During literature searches for cases, it may be possible to construct a search that excludes records for pharmaceutical forms or routes of administration different to that of the subject product. However, articles where pharmaceutical forms or routes of administration are not specified should be included in the search. Search construction should also allow for the retrieval of overdose, medication error, abuse, misuse, off-label use or occupational exposure information, which could be poorly indexed. Searches should also not routinely exclude records of unbranded products or records for other company brands.

Appendix 3.3.4Selection of search terms

As described previously, there is no acceptable loss of recall when searching published literature for pharmacovigilance. The use of search terms (free text or use of indexing) allowing the construction of more precise searches may assist in achieving more accurate results.

Common searching deficiencies include the following:

- the omission of outcome terms, for example ‘death’ as an outcome may be the only indexed term in a case of ‘sudden death’;
- the omission of pregnancy terms to find adverse outcomes in pregnancy;
- the omission of terms to include special types of reports which needs to be addressed as well in periodic benefit/risk assessment reports, for example,
    - Reports of asymptomatic overdose, medication error, off-label use, misuse, abuse, occupational exposure;
    - Reports of uneventful pregnancy.

Appendix 3.3.5Limits to a search

Some databases apply indexing that allows the application of limits to a search, for example by subject, age, sex, or publication type. The limits applied to a search are not always shown in the ‘search strategy’ or search string.

If limits are applied, they should be relevant to the purpose of the search. When searching a worldwide scientific and medical literature database, titles and abstracts are usually in English language.

Limits can be applied to produce results for date ranges, for example, weekly searches can be obtained by specifying the start and end date for the records to be retrieved. It should be remembered that the search includes an entire time period, for example, records that may have been added later in the day for the day of the search should be covered in the next search. The search should also retrieve all records added in that period, and not just those initially entered or published during the specified period (so that records that have been updated or retrospectively added are retrieved). This should be checked with the database provider if it is not clear.

Although one of the purposes of searching is to identify ICSRs for reporting, the use of publication type limits is not robust. ICSRs may be presented within review or study publications, and such records may not be indexed as ‘case-reports,’ resulting in their omission for preparation of periodic benefit/risk assessment reports from search results limited by publication type.

Appendix 3.4 Record keeping

Records of literature searches should be maintained in accordance with the requirements described in the Regulation. Marketing authorization holders should demonstrate due diligence in searching published scientific and medical literature. It is always good practice to retain a record of the search construction, the database used and the date the search was run. In addition, it may be useful to retain results of the search for an appropriate period of time, particularly in the event of zero results. If decision making is performed based on the results, it is particularly important to retain this information.

Appendix 3.5 Outputs

Databases can show search results in different ways, for example, titles only or title and abstract with or without indexing terms. Some publications are of obvious relevance at first glance, whereas others may be more difficult to identify. Consistent with the requirement to provide the full citation for an article and to identify relevant publications, the title, citation and abstract (if available) should always be retrieved and reviewed.

Appendix 3.6 Review and selection of articles

It is expected that the person reviewing the results of a search is trained to identify the articles of relevance. This may be an information professional trained in pharmacovigilance or a pharmacovigilance professional with knowledge of the database used. Recorded confirmation that the search results have been reviewed will assist in demonstrating that there is a systematic approach to collecting information about suspected adverse reactions from literature sources. It is recommended that quality control checks are performed on a sample of literature reviews / selection of articles to check the primary reviewer is identifying the relevant articles.

A common issue in selecting relevant articles from the results of a search is that often this process is conducted for the purposes of identification of ICSRs only. Because the review should also be used as the basis for collating articles for the periodic benefit/risk assessment report production, relevant studies with no ICSRs should also be identified, as well as those reports of events that do not qualify for reporting.

Outputs from searches may contain enough information to be a valid ICSR; nevertheless the article should be ordered. All articles for search results that are likely to be relevant to pharmacovigilance requirements should be obtained, as they may contain valid ICSRs or relevant safety information. The urgency with which this occurs should be proportionate to the content of the material reviewed and the resulting requirement for action.

Articles can be excluded from reporting by the marketing authorization holder if another company's branded medicinal product is the suspected medicinal product. In the absence of a specified medicinal product source and/or invented name, ownership of the medicinal product should be assumed for articles about an active substance. Alternative reasons for the exclusion of a published article for the reporting of ICSRs are detailed in 3.1.2.

Appendix 3.7 Day 0

Day zero is the date on which any staff member of a marketing authorization holder or contract organization becomes aware of a publication containing the minimum information for an ICSR to be reportable. It is sometimes possible to identify the date on which a record was available on a database, although with weekly literature searching, day zero for a reportable adverse reaction present in an abstract is taken to be the date on which the search was conducted. For articles that have been ordered as a result of literature search results, day zero is the date when the minimum information for an ICSR to be valid is available. Marketing authorization holders should obtain articles promptly in order to confirm the validity of a case.

Appendix 3.8 Duplicate reports

When reporting ICSRs, literature cases should be checked to prevent reporting of duplicates, and previously reported cases should be identified as such when reported.

Appendix 3.9 Outsourcing literature search services

It is possible to use the services of another party to conduct searches of the published scientific and medical literature. Even so, the responsibility for the performance of the search and subsequent reporting remains with the marketing authorization holder. The transfer of a pharmacovigilance task or function should be detailed in a contract between the marketing authorization holder and the service provider. The nature of third party arrangements for literature searching can range from access to a particular database interface only (access to a technology) to full literature searching, review and reporting (using the professional pharmacovigilance services of a contract pharmacovigilance service provider). It is recognized that more than one marketing authorization holder may share services of a third party to conduct searches for generic active substances. In this instance, each marketing authorization holder should ensure that the search and service is appropriate to their needs and obligations.

Where a marketing authorization holder relies on a particular service provider for literature searching, it is expected that an assessment of the service(s) is undertaken to determine whether it meets the needs and obligations. In any case, the arrangement should be clearly documented.

The clock start for the reporting of ICSRs begins with awareness of the minimum information by either the marketing authorization holder or the contract organization, whichever is earlier.

Appendix 3.10 Submission of copies of articles published in the scientific and medical literature

When a literature article refers to the description of more than one patient, the copy of the literature article should be sent only once.