TURKISH REPUBLIC
MINISTRY OF HEALTH
PHARMACEUTICAL GENERAL DIRECTORATE

# PHARMACOVIGILANCE GUIDELINES FOR REGISTRATION HOLDERS OF MEDICINAL PRODUCTS FOR HUMAN USE

**TURKEY PHARMACOVIGILANCE CENTER (TÜFAM)**

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# PHARMACOVIGILANCE GUIDELINES FOR REGISTRATION HOLDERS OF MEDICINAL PRODUCTS FOR HUMAN USE

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## SECTION I

### Legal Basis, Objective, Scope and Definitions

### 1. Objective

The objective of these guideline is to ensure safe usage of medicinal products for human use by ascertaining that adverse reactions are systematically tracked, data pertaining to this matter are collected, recorded, evaluated, archived, all pertinent parties are contacted, necessary precautions are taken in order to minimize any damage that may be caused by medicinal products for human use and to determine the principles and details with regard to the implementation of regulations currently in effect so that registration holders may conduct their activities and fulfill their obligations accordingly.

### 2. Scope

These guidelines encompass monitoring, research, recording, archival and evaluation activities which are conducted to ensure the safety of licensed/approved medicinal products for human use, content and method of required emergency and periodic reporting and minimum requirements for registration holders to continue their pharmacovigilance activities.

### 1. Legal Basis

These guidelines have taken as its basis article 22 of "Regulation Regarding the Safety Monitoring and Evaluation of Medicinal Products for Human Use", published on March 22, 2005 in Official Gazette no. 25763 and drafted to be implemented with the abovementioned Regulation.

### 2. Definitions

Definitions of terms mentioned in these guidelines have been alphabetically listed as follows:

**Adverse reaction / Adverse drug reaction**

Refers to a harmful and unintended effect that emerges during approved normal dose usage of a medicinal product for human use in order to protect from a disease, to diagnose or treat a disease or to improve, correct or modify a physiological function.

Within this framework, an adverse reaction is considered synonymous with a suspected adverse drug reaction.

Unlike an event, an effect is defined when a causal relationship between the drug and the occurrence is suspected, in other words, it is defined when a healthcare professional reporting or investigating the occurrence evaluates it as a possibility. Unless the reporter has specifically indicated a negative provision with regarding to the causal relationship, an effect reported as spontaneous generally indicates a positive provision by the reporter.

**Adverse event (adverse experience)**

Refers to an experience which arises subsequent to the implementation of a medicinal product. It is not necessary to establish a causal relationship between the undesired circumstance and the treatment.

**Minimum criteria for reportability**

In order to approve an adverse drug reaction t as "reportable", the following minimum information must be provided:

(a) A healthcare professional with a verifiable identity who is conducting the report

*The reporting individual's identity must be verifiable through his/her:*
*i) First and last names*
*or*
*ii) First and last name initials*
or
*iii) Address*
*and*
*iv) Profession (physician, dentist, pharmacist, nurse).*

(b) A patient with a verifiable identity

*The patient's identity must be verifiable through his/her:*
*i) First and last name initials*
*or*
*ii) Registration number*
*or*
*iii) Date of birth (if date of birth is not available, age)*
*or*
*iv) Gender. The data must be as thorough as possible.*

(c) At least one suspected substance / medicinal product

(d) At least one suspected adverse reaction.

Minimum data refers to the minimum amount of information that is required for the presentation of a report. Subsequently, necessary efforts must be made to gather and present detailed information as it becomes available.

Upon receiving information directly from a patient (or from a relative) claiming the possibility that a serious adverse reaction may have occurred, the registration holder must try to obtain pertinent information from a healthcare professional involved in the care of the patient. Upon gathering this data, the occurrence may be accepted as reportable. When a patient reports an adverse reaction and presents medical documents, if the documents meet the minimum data requirement and verify the patient's report, this should be considered sufficient to approve the effect as reportable.

**European Union Registration Date (EURD)**

Refers to the date that the first registration for a medicinal product was granted in the European Union (EU) to the registration holder.

*(EURD is the date that a registration was granted by the European Commission for a medicinal product which was registration within the scope of central procedures in the EU. For medicinal products which were licensed as part of mutually accepted procedures, the reference is the date when registration was granted by the member country.)*

**Unexpected adverse reaction**

Refers to an adverse reaction which does not conform with the Summary of Product Characteristics (SPC) of the medicinal product for human use in terms of attribute, severity or result.

In addition, it encompasses class-related effects specified in the SPC, which, however, have not been emphasized as occurring in relation to this particular product.

**Abuse of the medicinal product for human use**

Refers to a continuous or sporadic intentional over-use of a product, accompanied by harmful physical or psychological effects.

**Serious adverse reaction**

Refers to an adverse reaction which leads to death, vital threat, hospitalization or prolongation of hospitalization period, permanent or visible disability or incapacity to continue to work, congenital anomaly or birth defect.

Serious adverse reaction also encompasses serious undesirable clinical results related to usage beyond the Ministry-approved SPC (for instance, prescription for a higher dosage than suggested), overdosage and abuse.

When deciding whether an effect is serious in other circumstances, a medical evaluation must be conducted. Significant adverse reactions which do not pose any urgent vital threat or do not result in death, but may endanger the patient, must be considered as serious.

**CIOMS I Form**

Refers to the accelerated report form drafted by the CIOMS (The Council for International Organizations of Medical Sciences) I Working Group.

**World Registration Date (WRD)**

Refers to the date on which the first registration for a medicinal product was granted in any country in the world to the registration holder.

**Company Core Data Sheet (CCDS)**

Refers to the document prepared by the registration holder and presented in addition to the safety information, containing materials pertaining to indications, dosage, pharmacology and other product-related information,

**Company Core Safety Information (CCSI)**

Refers to all pertinent safety information, with the exception of those listed in the CCDS and circumstances wherein local administrative authorities request a particular change, that the registration holder deems necessary to list. CCSI has the attribute of being the reference information to help distinguish between "listed" and "unlisted" adverse reactions during the periodic reporting of products on the market. However, it is not used in determining the distinction between "expected" and "unexpected" adverse reactions with regard to accelerated reporting.

**Humanitarian Program on Early Access to Medicine**

Refers to an arrangement whereby, for humanitarian reasons, a non-registered medicine(s) is provided free of charge by the company which has developed the medicine to patients who have a serious or urgently life-threatening disease, whose treatment with registered and currently accessible medicinal products has been unsuccessful, and who are not able to have access to clinical research conducted in this area. In order to be included in this program, the product must have concluded its Phase II stage and proceeded to Phase III. *(This program is not a clinical drug research. These programs do not aim to gather data on the drug's effectiveness and, even if such data are collected, they may not be used in the procedures pertaining to the registration of the drug by the Ministry of Health.)*

**Listed adverse drug reaction**

Refers to an adverse reaction that, in terms of attribute, intensity, specificity and result, is in conformity with the CCSI.

**Unlisted adverse drug reaction**

Refers to adverse reactions which have not been specifically indicated as suspected adverse reactions in the CCSI and whose attributes, intensity, specificity and results are not in conformity with the information set forth in the CCSI. In addition, it encompasses effects related to the class of which the product is a member, mentioned in the CCSI, but whose occurrence in relation to this product has not been specifically indicated,

**Periodic Safety Update Reports (PSURs)**

Refers to the report whose content is regulated in these guidelines containing updated safety data pertaining to a registered/approved medicinal product for human use as well as a scientific evaluation report regarding the product's benefits and risks, which must be submitted by the registration/permit holder to the Ministry at intervals set forth by the "Regulation Regarding the Safety Monitoring and Evaluation of Medicinal Products for Human Use" published on March 22, 2005 in the Official Gazette no. 25763.

**Post-Registration/Permit Studies (PRS)**

Refers to all types of studies conducted within the framework of SPC conditions approved by the Ministry or under normal conditions of usage. With regard to the requirements of adverse event reporting and PSURs, the aforementioned post-registration studies refer to any type of post-registration studies that the registration holder is aware of.

**Post-Registration Safety Studies (PRSS)**

Refers to a pharmacoepidemiological or clinical studies, within the scope of PRS, aimed at defining or measuring safety risks regarding a registered/permitted medicinal product for human use and conducted in accordance with Ministry-approved registration/permit conditions for the particular product.

Any type of work wherein available safety data relating to the product will be significantly affected by the number of patient participants shall also be considered PRSW.

**Healthcare Professional**

Refers to a healthcare professional, namely a physician, pharmacist, dentist or nurse, involved in the reporting of a suspected adverse reaction.

*(If a report is drafted by a healthcare professional who is not a physician or dentist, whenever possible, a medically licensed individual should provide further details regarding the matter.)*

**Signal**

Refers to reported data regarding an unknown or heretofore insufficiently documented, potentially causal relationship between an adverse event and the medicinal product for human use. *(In order to issue a signal, more than one report is generally required, depending on the severity and quality of the notification.)*

**Contracted Pharmacovigilance Service Institution (CPSI)**

Refers to an academic, commercial or other type of institution, able to satisfy the conditions set forth in these guidelines and approved by the Ministry, with which the registration holder may share its obligations with regard to the safety of the medicinal product for human use specified in written form.

**Spontaneous notification**

Refers to the notification of a suspected adverse reaction which, during routine use of medicinal products for human use, occurs on a patient using one or more medicinal products for human use, and which has not emerged in any study, by a healthcare professional to the company and to TÜFAM by filling out the Adverse reaction Notification Form, or if the Form is not available, in writing.

**Data Lock Point (Data Cut-Off Date)**

Refers to the cut-off date by which data to be included in the PSUR must be incorporated in the report.

# SECTION II

## Registration Holders' Roles and Responsibilities, Transfer of Responsibilities

### 5. Registration Holders' Roles and Responsibilities

The registration holder must assume responsibility for his/her products on the market and must possess an adequate pharmacovigilance system so as to ensure appropriate execution of required procedures.

The fundamental responsibility of the registration/permit holder is to guarantee the safety of his/her products.

Therefore, in order to ensure that pharmacovigilance studies are effectively tracked and that the necessary pharmacovigilance system is established and maintained, the registration/permit holder is obligated to take all necessary precautions, including personnel training.

The registration/permit holder permanently employs a physician or pharmacist responsible for pharmacovigilance, with sufficient background in this matter, as an individual in charge of the safety of the medicinal product for human use. The registration/permit holder must provide the name, professional background and contact data of the individual he/she has hired as product safety officer (and individuals who will represent that individual in his/her absence), within a maximum of seven days following the date of hire, to Turkey Pharmacovigilance Center (TÜFAM).

The registration/permit holder ensures participation of the individual he/she as hired as product safety officer in training programs organized by the Ministry on pharmacovigilance or other programs deemed appropriate.

If different product safety officers are assigned to different products, this circumstance should be notified to the Ministry as set forth in the third paragraph. In the event this individual(s) changes, the individual(s) replacing them should be notified to the Ministry as set forth in the third paragraph of this article within a maximum of seven days following the date of hire.

Even if the registration/permit holder conducts his/her pharmacovigilance activities through a commercial, academic or scientific institution, he/she is required to employ a permanent product safety officer.

When registration holders enter into contractual agreements, arrangements conducted in order to satisfy pharmacovigilance requirements must be notified to Pharmaceutical General Directorate in clear terms, in writing on the date of registration and subsequently when a modification proposal is made to these arrangements.

With regard to two or more registered products with identical attributes except for their commercial names, each registration holder is required to satisfy his/her pharmacovigilance obligations.

### 5.1 Pharmacovigilance Unit

A pharmacovigilance unit must have the following minimum requirements:

1. It must employ at least one full-time pharmacologist, clinical pharmacologist or toxicologist or a physician or pharmacist who has successfully completed a training program in pharmacology organized by the Ministry or deemed appropriate as well as a sufficient number of appropriately trained auxiliary technical and support personnel. (Product safety officer may start his/her appointment upon participating in the first training program organized after his/her hire.)
2. It must possess a facility appropriate for conducting pharmacovigilance activities, a computerized communication system that is sufficiently automated, data gathering and processing abilities such as surveying and the like, a technical equipment adequate for organizing, managing and evaluating field studies, maintaining proper records and archives and collaborating with local, foreign and international institutions providing services in pharmacovigilance, data bases and data networks as well as documents on standard work methods regarding these tasks.
3. It must have written programs to ensure continuous technical training of personnel.
4. It must maintain a file documenting the service-related training that each technical employee has undergone.
5. It must allocate a special location for archives and employ an archivist.

### 5.2 Transfer of Responsibility to a Contracted Pharmacovigilance Service Institution (CPSI)

The registration holder may satisfy the obligations associated with pharmacovigilance, arising from these guidelines and regulation, through an intermediary PSIC in compliance with the following principles. Under such circumstances, a notarized division of responsibility document must be presented to the Ministry.

In addition to the above-mentioned five articles, the CPSI must meet the following requirements pertaining to the minimum number of technical employees and technical equipment as outlined below:

6. When there is an increase in the number of companies with which it shares obligations and in the number medicinal products which are under its responsibility, it must increase its personnel size and equipment in proportion to its workload.

7. It must file different company products in distinct archive locations and must specify company employees in charge.

In order to commence its activities, CSPI must submit an application file to the Ministry, proving that it meets the abovementioned personnel, facility, equipment and other requirements and including contact information.

CSPI may commence activity upon receiving approval from the Ministry subsequent to its inspection of the file or, if deemed necessary, subsequent to its inspection on site.

If there is any personnel change at CSPI, newly hired individuals must be reported to the Ministry within a maximum of seven days.

**6. Responsibilities of the Safety Officer for the Medicinal Product for Human Use**

It is the product safety officer's responsibility to forward all information, including information gathered from post-registration studies relating to the evaluation of a medicinal product's risks and benefits, to Pharmaceutical General Directorate.

He/she is responsible for:

a) Establishing and managing the necessary system for conducting pharmacovigilance activities, preparing, updating and implementing standard pharmacovigilance work methods necessary for monitoring and evaluating all suspected adverse reactions that have reached company personnel, including medicinal sales representatives,

b) Gathering, recording, archiving and evaluating information pertaining to the risks and safety of medicinal products and ensuring that all medicinal product registration files contain updated information in this regard,

c) Planning and conducting post-registration safety studies, gathering necessary data, recording and evaluating obtained results,

d) Informing TÜFAM of the data gathered as a result of studies and announcements,

e) Upon request of the Ministry, immediately providing thorough and fluid answers to requested data including information pertaining to the sales or prescription volume of the product in question to be able to conduct an evaluation of the product's benefit and risk balance,

f) Establishing the requisite cooperation and coordination with the Ministry,

g) Providing the Periodic Safety Update Reports as well as other information and documents requested by the Ministry in a timely manner,

h) Other activities pertaining to the management of the company pharmacovigilance mechanism, hence, briefing and training of all concerned personnel including medical sales representatives regarding the monitoring of adverse reactions and their responsibilities, ensuring the participation of concerned personnel in training events organized or approved by the Ministry.

The Product safety officer conducts these activities in accordance with pertaining legal provisions.

The Product safety officer must be knowledgeable about current publications by utilizing widely used reference and literature research databases (such as Medline, Excerpta Medica or Embase) no less than once a week (no less than once a month for Turkish data searches) or through intermediary contracted pharmacovigilance service institutions.
The registration holder must provide the necessary infrastructure that will enable proper examination of concerned publications.

## SECTION III

## Reporting

### 7. Reporting of Adverse Reactions

The registration holder is responsible for notifying Pharmaceutical General Directorate of suspected adverse reactions in a manner as specified in this section.

### 7.1 Scope

With respect to registered medicinal products for human use, suspected adverse reactions as notified by healthcare professionals must be reported.

The following are subsumed within this scope:

- Suspected adverse reactions reported as spontaneous
- Suspected adverse reactions emerging in post-registration studies
- Adverse reactions reported in world literature

If the reporting healthcare professional or registration holder believes that there is a causal relationship between the drug in question and the effect, from a causal relationship point of view, that effect is considered at least suspect. Spontaneous suspected adverse drug reactions notified by healthcare professionals must be reported even if the reporting registration holder does not agree with the assessment of a causal relationship or even if the reporting individual has not presented an assessment of causality. Adverse events deemed to be unrelated to a drug by a healthcare professional involved in the patient's treatment should not be reported as long as the registration holder sees no perceptible rationale for a causal relationship.

If a registration holder has absolute knowledge that a healthcare professional has reported an adverse reaction associated with one of his/her products directly to TÜFAM, the registration holder choose not to report this effect in order to avoid a reiterated notification. If he/she chooses to file a report, in such cases, he/she must warn TÜFAM that this report might be a replica of a prior report. In such cases, the registration holder must provide all available details to TÜFAM in order to assist in the identification of the repeated report. The registration holder must also provide TÜFAM with any additional gathered data regarding the previously reported adverse reaction.

Registration holders must verify and track all serious adverse reactions they have reported to TÜFAM. All available clinical data pertaining to the evaluation of the effect must be presented. If the adverse reaction is serious, its follow-up must be conducted in accordance

with the notification period for serious adverse reactions. However, in adverse reactions resulting in death or vital threat, every necessary effort must be made in order to provide monitoring data pertaining to the event (in the shortest possible period of time).

### 7.2 Requirements for Accelerated Reporting

All serious adverse reactions meeting the minimum criteria for reportability must be reported in a series within at most 15 days subsequent to receiving notification.

The period for Accelerated Reporting commences when one or more of the following individuals receive the minimum data necessary for presenting an adverse reaction report:

- Any employee of the registration holder including sales representatives,
- Safety Manager for the Medicinal Product for Human Use or individuals working with this authority,
- In instances where the registration holder has a relationship with a second company (such as co-marketing, institution under contract, etc.) with regard to the marketing or research of the suspected product, any employee of the registration holder *(administrative notification must not exceed 15 days after the second company receives the data. In order to ensure satisfaction of these requirements, a detailed and clear document on the division of responsibility must be signed by the registration holder and the second company.)*
- In instances where, on a global scale, pertinent scientific literature can be located, any employee of the registration holder who is aware of the publication.

#### 7.2.1 Case Reports on Spontaneous Adverse Drug Reactions

#### A. Adverse Reactions Requiring Accelerated Notification

#### i) Serious Adverse Reactions Occurring In Turkey

The registration holder must report all serious adverse reactions, occurring within the borders of Turkey and indicated to him/her by a healthcare professional, to TÜFAM on an accelerated basis.

Suspicious increases in the frequency of serious adverse reactions must also be reported on an accelerated basis. The basis upon which the frequency evaluation is conducted must be specified.

#### ii) Serious Adverse Reactions Occurring Outside Turkey

It is sufficient for the registration holder to include notifications of occurrences outside the borders of Turkey, indicated to him in any manner, in the following periodic safety update report. However, if these reports modify the familiar risk/benefit profile of the product (safety warnings issued in any country of the world, safety-related changes made in the product's currently effective SPCs in the sections pertaining to counter-indications and warnings/precautions, indication restriction, recall, suspension, registration cancellations, etc.), without exception, TÜFAM must be immediately notified within a maximum of 15 days subsequent to receiving the information in question.

Upon TÜFAM's request, the registration holder must immediately provide adverse reaction reports originating in foreign countries, which play a role in such decisions.

**B. Other Spontaneous Adverse Drug Reactions**

All other adverse drug reaction reports must be provided within the Periodic Safety Update Report in a sequential list unless TÜFAM requests otherwise.

### 7.2.2 Case Reports

The registration holder is expected to be current and knowledgeable about global literature.

The registration holder must follow and archive global scientific literature and must report published suspicious serious adverse reactions occurring inside the borders of our country, pertaining to the use of active ingredient/ingredients within his/her own medicinal products, in accordance with the categories specified in these guidelines.

In particular, forwarding national or international publications which involve data pertaining to our country's population as well as notifications and posters is extremely important. A copy of the pertinent article, along with a Turkish translation of the whole article or its summary, must be submitted in the original language.

### 7.2.3 Post-Registration Study Reports

All serious suspicious adverse reactions occurring in post-registration studies, which the registration holder is aware of, must be reported on an accelerated basis to the pertinent unit of the Pharmaceutical General Directorate (Clinical Pharmaceutical Research Unit / Observational Studies Unit) by taking into account the source (Phase IV Research / Observational Epidemiological Studies). *(The pertinent unit coordinates sharing of information with TÜFAM).*

Blind cases and adverse events deemed to be unrelated to work products must not be reported as spontaneous reports. Blinded cases where serious unexpected adverse reactions were encountered must be resolved by the sponsor prior to reporting. One may report expected serious effects on an accelerated basis only if the blinding has been resolved through any other means. Apart from these instances, cases where serious unexpected effects were encountered in blinded works must be urgently reported immediately following the resolution of the blinding. Non-serious adverse events must be included in the outline of post-study reports; they do not need to be reported separately.

Provisions of the Regulation Regarding Pharmaceutical Research, published on January 29, 1993 in the Official Gazette, No. 21480 and the Good Clinical Practice Guidelines will apply to reports drafted in post-registration studies with clinical research attributes. Reports relating to observational epidemiological studies shall comply with pertinent regulations.

The active ingredient/product name in each spontaneous adverse reaction case report shall be specified as indicated in the report drafted by the first reporter.

Original words used by the reporter in describing the adverse reaction must be written and, if necessary, must be translated into Turkish.

The registration holder is expected to track all reports pertaining to serious suspicious adverse reactions associated with his/her own products in order to be able to access pertinent information whenever possible. New information which was not available during the drafting of the first report must be presented in the form of follow-up reports.

**7.3 Reporting Forms**

With regard to the notification of adverse reactions, the Adverse Reaction Notification Form, prepared by TÜFAM and specified in paragraph 1, article 4 of the Regulation Regarding the Safety Monitoring and Evaluation of Medicinal Products for Human Use, published on March 22, 2005 in the Official Gazette, no. 25763, must be used. (See Annex I) In the event that the form is not available, written notifications are acceptable. Computer-generated forms may be acceptable so long as they are legible and comply with the appropriate content and organization.

With regard to vaccinations, the "*Post-Vaccination Unwanted Effect Notification and Examination Form*", set forth in the addendum to the general regulation of Post-Vaccination Unwanted Effect Monitoring System, No. 2003/127-16513, put into effect by the Ministry of Health of the Turkish Republic Basic Healthcare Services General Directorate on November 3, 2003 upon its publication, and updated as deemed necessary, must be used.

The following information as requested in the Adverse Reaction Notification Form in Annex 1 must be supplied as thoroughly as possible. When deemed necessary, it is possible to include additional pages to the form in order to provide further information or to include items considered to be pertinent, but which may not fit into the contents of the form.

Registration holders may provide their opinions as to whether they think there may or may not be a causal relationship between suspicious product(s) and reported adverse reaction(s). In such instances, they must specify the criteria they have used in conducting their evaluation. In this regard, they submit the CIOMS I Form, found in Annex II, in addition to the notification form.

A. PATIENT-RELATED INFORMATION

1. First and last name initials
2. Date of birth
   If date of birth is unknown, age
3. Gender
4. Height (in cm)
5. Weight (in kg)

B. INFORMATION REGARDING THE ADVERSE REACTİON

1. Description and intensity of the adverse reaction *(When conducting this description, medical terminology must be used as much as possible. Such as pruritus, apnea, urticaria, etc...)*

- Starting date of the adverse reaction (should be notified as day, month, year.)
- Ending date of the adverse reaction (should be indicated as day, month, year.)
- Result of the adverse reaction (not the result of the disease treatment but the result of the result of the adverse reaction which has occurred should be indicated.)

2- criteria of severity (if death has occurred, the reason of death should be classified according to ICD-10. If autopsy has been conducted, the findings of the autopsy of the autopsy report should also be attached. It should not be forgotten that death is not an adverse reaction but a consequence.)

3- laboratory findings (with pertinent dates)
4- relevant medical story/concomitant diseases (any association information which may help to evaluate the case (allergy, pregnancy, excessive consumption of cigarettes and alcohol, hepatic/renal impairment, diabetes, hypertension,...) should be added. With regard to congenital anomalies, all drugs taken by the mother during pregnancy as well as the diseases she has been exposed to should be indicated with the last period of date).

C. INFORMATION REGARDING MEDICINAL PRODUCTS USED:

1- name of suspected medicinal product; INN name is the commercial name is not known,
2- route of administration,
3- daily dosage (relevant calculation should be performed with regard to drugs administered with a mg/kg calculation or $m^3$ calculation. In drugs used for curing, the curing session when the adverse reaction was observed should absolutely be indicated.)
4- date of starting the drug (should be indicated as day, month, year.)
5- date of stopping the drug (should be indicated as day, month, year. If the use of the drug has not been stopped, state CONTINUE. If the dates when the drug has been used is not certain but a certain timeframe may be indicated (such as 3 weeks, 2 days) indicate this period.)
6- for which indication has the drug been used (indicate for which indication the drug has been used without making any abbreviations. In the notifications to be conducted by the companies, they are expected to classify the drug being used in accordance with ICD-10. Also the healthcare professionals working in the hospitals which use this classification system are expected to make a classification in accordance with ICD-10).
7- Information on whether the use of drug has been stopped at the emergence of the adverse reaction (the elimination of the interference).
8- Information on whether the adverse reaction has decreased if the use of the drug has been stopped or the dosage has been decreased.
9- Information on whether the drug has started to be used again upon the elimination of the adverse reaction pursuant to stopping the use of the drug at the emergence of the adverse reaction (re-interference)
10- Information on whether the adverse reaction has recurred after starting to use the drug again
11- With regard to concomitant drug(s)

Also all drugs (where possible) which have been used in the previous month before the emergence of the adverse reaction should be notified. There may be associations even in longer periods in some adverse reactions such as aplastic anemia, fibrotic effects and cancer. Also non-prescription drugs, magistral preparations, herbal products and products used as dietary supplements should be included according to their degree of association. Nutrients likely to enter into interaction in terms of drug-nutrient interaction should also be mentioned. With regard to concomitant drugs, the name, route of administration, daily dosage, date of starting and stopping the drug and the indication (ICD-10) should also be indicated.
The drugs used for the treatment of adverse reaction shall not be regarded as concomitant use, thus they should not be indicated in the section of this type of drugs.

12. Other observations and comments:

Should there be any suspicion with regard to quality problems arising from the manufacturing or storage conditions, the relevant problem, the batch number of the drug as well as the expiration date should be indicated.

13. The methods and drugs used for the treatment of the adverse reaction should be indicated with the dates they have been used.

D. INFORMATION REGARDING THE PERSON MAKING THE NOTIFICATION:

1- name and surname
2- profession
3- telephone number
4- address
5- fax number
6- e-mail address
7- signature
8- whether the report has been communicated to the relevant company
9- report date
10- type of report (initial, follow-up) (in follow-up reports, the date of the initial report and where available the registration number issued by TÜFAM should also be indicated.)
11- medical registration no.

E. INFORMATION ON THE REGISTRATION/PERMIT HOLDER
(to be filled only in case of notifications conducted by the registration/permit holder).

1- name and contact information of the registration/permit holder (tel., fax, address)
2- contact information of the product safety officer, including name and surname, e-mail, signature
3- report number of the registration/permit holder
4- date when the registration/permit holder was first informed
5- notification date of the report to TÜFAM
6- report type
7- source of report (outside of Turkey, consumer, observational study, literature, healthcare professional, from an institute, outside an institute, registration holder, others,...)(more than one option may be selected)

### 7.4 Impact of the report adverse reactions on a product's general safety profile and its summary of product characteristics

In exceptional cases where a report adverse reaction has had a serious impact over the determined safety profile of a product, for instance in cases such as the following:

- relation with a series of similar or associated events reported simultaneously,
- first degree evidence of a causal relationship associated with a serious or unexpected reaction,
- claim about a modification in the character, severity or frequency of an expected adverse reaction,
- presence of new definable risk factors,

the registration holder should indicate these in the report.

Information pertaining to the frequency of adverse reactions should use comprise the basic data used in frequency estimations (such as total number of adverse reaction reports and data on number of patients exposed).

In cases where the reported adverse reactions have an impact over the determined safety profile, the registration holder should indicate the type of transaction proposed with regard to the product registration and summary of product characteristics.

## 8. Reporting Requirements Under Special Circumstances

Regardless of whether the medicinal product is used in compliance with the approved summary of product characteristics (for instance, including the doses prescribed higher than the recommended dosage), adverse reactions should be regarded as reportable in accordance with the requirements of the section on accelerated reporting. (See Subsection 8.7 with regard to the reporting requirements on excess dosage).

### 8.1 Reporting within the period between registration application and issuance of the registration

In the pre-registration period, any information to be submitted by;

- the application holder,
- any country where the drug is used within the scope of the Humanitarian Program on Early Access to Drugs,
- and that may affect the benefit/risk evaluation to be submitted by the countries where the drug is registered, shall forthwith be communicated to TÜFAM.

Accelerated spontaneous reporting shall not be required in other cases, during the period between the registration application and the issuance of registration, except for cases when the product is used in clinical studies.

### 8.2 Parameters which may cause modifications in the risk/benefit information:

- A report pertaining to an expected/new serious suspected reaction, comprising a valid evidence on the presence of a causal relationship,
- Reports pertaining to a series of adverse reaction cases, comprising a potential relationship,

- Adverse reaction reports comprising suspicions of a modification in the severity or frequency of a known reaction.
- Studies which may modify the profile of effectiveness.

In these cases, the registration holder should conduct the relevant changes pursuant to an evaluation concerning the risk/benefit condition and forthwith notify TÜFAM.

### 8.3 Reporting of results pertaining to use during pregnancy

Registration holders are exported to follow up all reports prepared by healthcare professionals, pertaining to the pregnancies where the fetus may have been exposed to one of their medicinal products for human use. If the reports have been drafted by a patient, reasonable follow-up studies should be conducted on the relevant patient by a healthcare professional. In case of a long half-life of an active substance or one of its metabolites, this condition should be taken into consideration when evaluating whether the fetus may have been affected (i.e., the medicinal products taken before the gestational period should be evaluated).

Congenital anomalies that the healthcare professional thinks may be stemming from the teratogenic effect of the drug have to be processed as an accelerated report and reporting requirements should duly be complied with.

These events as well as other reports concerning anomalies in pregnancy, details of normal/abnormal results, together with all data on total exposure should be included in the PSUR. Reports taken from prospective records should also be included in the PSUR and evaluated therein.

If, in the period between PSURs, a registration holder notices a signal of teratogenic effect (for instance, if he notices a series of similar abnormal pregnancy results), TÜFAM should forthwith be notified.

### 8.4 Reporting Pertaining to Other Post-Registration Data Collection Activities: Surveys and Patient Registering Systems

A registration holder may undertake activities after registration that enable collection of information about products. In such cases, there should be a differentiation made between studies where there is a systematic process to report adverse reactions to the registration holder and those studies where there is not. Only, events that have been reported as suspected serious adverse reaction related to a specific drug are subject to accelerated reporting. Reporting requirements should be handled as in accelerated reports from post-registration studies.

### 8.5 Humanitarian Program on Early Access to Drugs / Off-label Use (Personal Treatment Drugs)

#### 8.5.1 Humanitarian Program on Early Access to Drugs

Use of a drug through Humanitarian Program on Early Access to Drugs should be strictly controlled by the company liable to procure the drug, and should be subject to a protocol. The protocol should enable the patient to be registered and sufficiently informed

about the composition of the drug; and in order to maximize probability of safe use, available information on the drug's properties should be given both to the doctor prescribing the drug, and to the patient. The protocol should encourage the physician prescribing the drug to report all kinds of adverse reactions suspected to be related to the drug's use to the company and the Department of Clinical Studies. Companies should continually monitor the benefit/risk ratio of the drugs used under such conditions. All adverse reactions stemming from the Humanitarian Program on Early Access to Drugs should be announced to the relevant department (Department of Clinical Studies).

### 8.5.2 Off-label Use (Personal Treatment Drugs)

In Turkey, TÜFAM should be notified, in accordance with the deadlines stated in these guidelines, of all medicinal products for human use that are unregistered/non-permitted, but are permitted to be imported for personal treatment; and adverse reactions appearing during off-label use of registered products for personal treatment purposes and through prescription approval.

### 8.6 Ineffectiveness

Ineffectiveness reports are not normally required to be accelerated, but is sufficient to be stated in the relevant periodical safety updating report. However, in certain situations, ineffectiveness reports should be treated as an accelerated event for reporting purposes:

- Medicinal products for human use that are used in treatment of potentially fatal diseases
- Vaccines
- Contraceptives

are examples of medicinal product categories where ineffectiveness has to be handled as an accelerated report. During reporting, an evaluation including decision should be made. For instance, if the medicinal product is in reality not suitable (not indicated) for the infective agent, antibiotics used in potentially fatal situations should not be reported. Only potentially fatal infections, if it's thought that the ineffectiveness depends on the development of a resistant bacteria strain that was previously considered sensitive, should be reported in acceleration.

Ineffectiveness in anti-neoplastic agents, if the said ineffectiveness does not indicate a change in the benefit/risk ratio – for instance, if it does not indicate an unexpectedly low effectiveness or a higher than expected figure or ratio in fatalities resulting from an advancing disease- should not be reported in a routine pattern like an accelerated report.

### 8.7 Reporting of overdosage and abuse

Situations indicating suicidal tendency and subsequently those indicating the suspected drug or other drugs causing overdosage should be accepted as adverse reactions and should be reported to TÜFAM within the reporting period and procedures indicated in the guide.

Other than that, reports regarding overdosage unrelated to adverse reaction (*for instance, consumption by accident or suicide attempt for reasons other than drug [psychopathological reasons]*) and abuse should not be reported as adverse reaction; but

should be notified as a periodic ranking list. There should also be a part including patient monitoring and intoxication results in the list. For confirmation that such situations are not adverse reactions, information on early indications, treatment, and result should be monitored as regularly as possible.

### 8.8 Reporting on Misuse

The registration holder should collect information about misuse of his products that may influence the benefit/risk evaluation; and should report in acceleration to TÜFAM all instances of misuse causing suspected serious and unexpected adverse reactions in Turkey, or serious and unexpected adverse reactions changing the risk/benefit profile of the drug occurring outside Turkey.

## SECTION IV

## Periodical Safety Update Reports

### 9. Presentation of Periodical Safety Update Reports

When a product is registered in Turkey, even if it's not being marketed, the registration holder should present a PSUR.

During the presentation of PSURs to TÜFAM, registration holders, in the light of new or changing post-registration information, are expected to present a serious evaluation of summary product characteristics and the benefit/risk ratio of the product. It should be clearly stated in this evaluation whether there is a need for further research or for any changes in the registration, short product characteristics, patient guidelines, or product information.

PSURs shall be accepted as hard copy, or in PDF format.

### 9.1 Presentation Periods

Under normal conditions, PSURs should be prepared every six months for the first two years pursuant to the registration of the medicinal product; then annually for the following two years; and for 5 years at the first renewal and for each subsequent renewal. However, there might be exceptions to waive the PSUR requirements when the period is started again, or for biannual or annual reports. These exceptions have been explained in 9.2.3.3.

### 9.2 General Principles

Administrative information in registration applications and renewals, and unlisted serious adverse reactions should be listed in cumulative summary tables both for the relevant period, and also starting from World Registration Date. All other relevant clinical and non-clinical safety data should include only the report period.

The theme of the report should be the adverse reactions of the drug. If the medical professional preparing the report has not stated otherwise, all adverse reaction experiences reported spontaneously should be accepted as drug adverse reactions. Experiences in clinical studies and literature cases that have been decided as irrelevant to the drug by both the reporter and the manufacturer/sponsor should be excluded.

Particularly ineffectiveness reports on drugs that are used in treatment of potentially fatal conditions and other medicinal products, such as contraceptives and vaccines may indicate a serious danger; and from this standpoint, might be accepted as a safety issue. Such cases should be discussed in the PSUR.

An increase in the reporting frequency of known adverse reactions are generally considered as relevant new information. Such an increase in reporting should be mentioned in the PSUR. Although there is no single standard stating what is the measure of over-reporting or which method is more appropriate for explaining the subject in figures, registration holders should give details about the methods used. There should be an opinion stated in the report as to whether the data indicate any change in formation of adverse reaction or a meaningful change in the safety profile; and whether an explanation (*for instance, the group affected, period affected*) may or may not be suggested for such a change.

### 9.2.1 Products containing a single active substance

Under normal conditions, all dosage forms and formulas of medicinal products registered in the name of a single registration holder, and indications of a certain pharmacological active substance may be included in a single PSUR. Below the same PSUR, making separate presentations for data on different dosage forms, indications, or user group (for instance, children vs adults) may offer convenience in inspection.

For a new registration for a product containing the same active substance *(different dosage, different form, different route of administration, etc)* with a product registered in the name of the registration holder, data lock points used in the PSURs should also be used in the joint PSURs including subsequent products. However if, under normal conditions, other conditions have not been stated in the clauses for granting the registration, the period of presentation shall start again with the granting of the new registration. In such a situation, joint PSURs presented in accordance with the latest registration period include data concerning all previous products.

### 9.2.2 Combined Products

For a combination of substances registered as a single active substance, depending upon conditions, safety information on the fixed combination may be reported in a separate PSUR, or may be included as a separate presentation in the report of one of the different components. All relevant PSURs must refer to each other.

### 9.2.3 Frequency of inspection and reporting

#### 9.2.3.1 PSUR reporting requirements

Unless it is stated otherwise on the registration (See subsection. 9.2.3.2 and 9.2.3.3), PSURs should be presented to TÜFAM in the following terms, starting from EURD:

- Immediately upon request
- Biannually in the two years pursuant to registration
- Annually in the subsequent two years
-At the first renewal
- For 5 years at the subsequent renewal

The birth date of products not registered in the EU is the World Registration Date.

#### 9.2.3.1.1 National report

Apart from PSUR compatible with EURD or WRD, companies should submit an additional report including national data. The following methods are applied for terms of national additional reports:

1. For the first two years, national report (or PSUR) is presented every six months
2. Subsequently, PSUR presentation is done based on ABRT or DRT, and in synchronization with the EU or World period terms. (In case the PSUR of this period including information to be given in the national report, national report may not be presented)

Presentation of a national report concerning only products registered in our country, and including only national data is sufficient.

Minimum information to be included in the contents of the national report is listed below:

- Introduction
- CCDS: Company Core Data Sheet (if different from the PSUR, including the latest copy of the CCDS document)
- Important decisions concerning drug safety
- Ranking lists and/or summary tables
- Conclusion *(a short review of new information and any effect on the known drug safety profile)*

### 9.2.3.2 Registration Renewals

The registration holder, along with renewal application, should present the PSUR at least 3 months before the validity of the drug's registration in Turkey expires. This presentation may be realized beforehand to facilitate coordination with the PSURs regular period.

Registration holders should lock their data latest by 60 days before presenting the renewal application. PSUR should include the period from the last PSUR. For the first renewal, the most recent biannual PSUR should be submitted; in the subsequent renewal, a single 5-year PSUR or the PSUR explained in subsection. 9.4, together with a bridge summary report, annual or biannual PSURs covering 5 years may be presented.

### 9.2.3.3 Circumstances under which where PSUR presentation periods may be modified

- In certain situations, PSUR submission with a greater frequency may be requested as a condition for registration. In some special situations, a less-frequent presentation may not constitute a problem.
- In any case, it's not possible to submit PSURs less frequently than once every five years.

- In case of a period of over a year between the launch of a product anywhere in the world and its registration date, the PSUR period may be revised. In order to be able to determine the subsequent order of PSURs, in the year before the first launch, the anniversary of the drug's birthday may be selected. For instance, for a drug that was registered in the 10$^{th}$ month of 2004 and launched in 2006, the birth date may be chosen as the 10$^{th}$ month of 2005.

#### 9.2.3.4 Preparation of PSURs in accordance with the World Registration Date

WRD is used for medical products registered outside the EU. WRD expresses the date the first registration was granted for the product to the registration holder anywhere in the world. For products that were registered first in the EU, EURD and WRD are naturally the same. If the registration holder prefers, for administrative convenience, WRD may be determined as the last day of the same month. For products that are registered in Turkey for the first time in the world, the Turkish birthday is also the WRD.

In order to make periodical safety updates compatible on an international basis, the registration holder may use DRT instead of EURD to determine data lock points in Turkey. If WRD is used, on the condition that other requirements have not been determined during granting the registration, the first data lock point must be within the six months following the date of the EU Marketing Authorization. Regardless of use of WRD or EURD, the PSURs should always be presented within the 60 days following the data lock point.

#### 9.2.3.5 Granting an additional period for PSUR presentation

In rare cases, the registration holder may request an additional period from the Pharmaceutical General Directorate for presenting the PSUR. Ideally, this request should be made before the data locking point.

Such a request should rest on valid reasons. Extension of the said period may, for instance, be requested in the following situations:

- The number of new events notified during the term included in the report being too many regardless of a new and significant drug safety concern.
- In case there is any new information present in the previous PSUR that the registration holder or the Pharmaceutical General Directorate wish to include in the subsequent PSUR.

### 9.2.4 Reference safety information

The purpose of the PSUR is to determine whether the information recorded in the reporting period is compatible with the previous information on the safety of the medical product and to state whether there is a need to make any changes in the product characteristics. In order for this comparison to be made, reference information is required.

The registration holders use as reference the CCSI within the CCDS that includes other information on safety, indications, determining dosage, and pharmacology.

The CCSI constitutes the basis in determining the listed or unlisted adverse drug reactions. Summary of Product Characteristics, on the other hand, continues to be the reference document forming the basis of expectancy (differentiation of adverse reactions) from the point of view of reporting after local accelerated registration.

In the application enclosed to the PSUR, it's important to emphasize the differences present between the CCSI and the SPC in Turkey/ the patient leaflets in Turkey.

The CCSI valid at the start of the reporting period should be used as reference for the biannual and annual reports.

The lists, at the time the PSUR is prepared, when evaluated after the data locking point, are generally accepted on the condition that the CCSI is used as the source document, and this being clearly stated in the PSUR text. During continuous evaluation by the registration holder of the lists at the event introduction and during the report period, current CCSI version should be used, and in case there are any changes made in the lists in time, their reasons should be explained. In both cases, changes made in the CCSI since the previous PSUR should be explained in subsection. 9.3.4 (change in the reference safety information) and/or in "General Evaluation of Safety".

During preparation of a PSUR with a period longer than a year, or of a bridge summary report, it's not practical to use the CCSI list analyses valid at the start of the period. There might be important changes made in the lists during the period, in accordance with the evaluation method. In this case, the most recent CCSI valid at the end of the reporting period might be used. The registration holder should guarantee explanation of all changes made in CCSI during the period in the PSUR, subsection. 9.3.4.

### 9.2.5 Data presentation pertaining to individual event stories

#### 9.2.5.1 Sources of information

In general, data received from the following four adverse reaction event information sources are potentially sources accessible to the registration holder, and should be included in the PSUR:

i. Reportings made directly to the registration holder (or under the registration holder's control):

a- spontaneous notifications of health professionals

b- clinical studies supported by the registration holder, off-label personal treatment drugs based on prescription approval, or the Humanitarian Program on Early Access to Drugs

ii. Literature

iii. Drug adverse reaction reporting systems of administrative authorities

- spontaneous notifications and non-spontaneous notifications

iv. Other data sources:

a- adverse reaction reports exchanged between contracted sources (ie, licensor and registration holder)

b- special record data such as the data found in organ toxicity monitoring centers

c- reports compiled by poison control centers

d- epidemiological databases

#### 9.2.5.2 Defining an Adverse Reaction

The adverse reaction terms used in the PSUR are in general taken from the standard terminology used by the reporting registration holder.

If possible, in order to define adverse reaction, the adverse reaction terms of the reporter making the submission should be used. However, if the terms of the notifying reporter are medically not appropriate or meaningful, registration holders, in order to enable the most correct possible use of original terms, should use the most appropriate adverse reaction terms in their own terminology. In such a case, the following points should be considered:

-In order for the information given by the submitting reporter to be accessible on demand, this information should be kept in a file word by word, in its original language along with its Turkish translation.

- If the registration holder does not agree with the diagnosis of the notifying health professional, he can mention this disagreement in the part where the events are listed.

- Registration holders should report and try to understand all information on the example case report. For instance, there might be shown a laboratory anomaly not mentioned/evaluated by the notifying reporter.

For this reason, when necessary and appropriate, both definitions of the finding, indication, or diagnosis may be given in the listed order:

- Either the original reported version of the adverse reaction; or,

in case of a discrepancy, medical interpretation of the registration holder (should be denoted by an asterisk or another means.)

### 9.2.5.3 Ranking Lists and/or Summary Tables

Present adverse reaction events should be presented, according to their sources and types, as a ranking list and/or summary table. (See Table 3.2 and 3.3 in Annex 3).

It shall be sufficient for this ranking list to include key information collected on events; it does not have to contain all the details. However, when necessary, the Ministry shall demand to see all event reports related to the effects, which are wished to be investigated comprehensively.

The registration holder should prepare a standard listing form including those events directly reported to themselves (See subsection 9.2.5.1.i), in addition to the events notified by the Ministry. The same should be done for published literature; and if the literature has not been documented well, the author should be contacted to try and collect adequate information. In addition to this, including data on spontaneous reports from second or third sources are;

1. Not possible before the standardization of data elements.
2. Not appropriate because of the possibility to include duplicated, incomplete or irrelevant information.

For these reasons, under such conditions, summary tables or concise compilations should be considered acceptable.

Apart from ranking lists of individual events, summary tables of adverse reaction terms used for findings, symptoms, and diagnoses in all patients should be presented in a way as to offer a general point of view. In these tables, apart from the data in the ranking lists (for ex. All serious adverse reactions and all non-severe unlisted adverse reactions), events not

requiring to be listed (for ex. Non-serious listed adverse reactions) should be taken as a basis. The details are given in subsection. 9.3.6.3 and 9.3.6.4.

## 9.3 Sample Periodic Safety Update Report (PSUR)

The paragraphs below have been compiled as a sample PSUR. Information is given on what should be stated in each part. Because PSURs contain registered information, it should be noted on the cover that the information given in the report and the results are confidential.

In order for the reader to be able to peruse quickly the most important information, the registration holder should prepare a summary for each PSUR, a sample of which is given in the CIOMS V report. This summary should be presented at the beginning of the PSUR, immediately after the cover page.

### 9.3.1 Introduction

The registration holder should make a short presentation of the product in the introduction. This presentation should enable the report to be both meaningful in itself, and relevant to the previous reports and conditions.

Not only the product(s) included in the report, but also (if any) product(s) that are excluded must be indicated. An explanation should be made about the products excluded (for instance, it should be noted that these will be analyzed in another report (as in a combined product)).

### 9.3.2 Global Registration Status of the Product

In this part of the report, cumulative information is given. In all countries where there are administrative decisions taken for registration, the following information should be given in a table:

- Date of the registration and of the subsequent renewal
- All kinds of characteristics restricting the registration; for instance, if concerning safety, limits on indications
- Treatment indications and special target groups within the scope of registration
- Whether there is any registration limit in any country; if yes, the reason
- Registration holder's recalling the registration application because of safety and effectiveness
- Launch dates of the products
- Commercial name(s) of the products

In general, indications of use, target group treated (for instance, children and adults), and dosage forms shall be the same in many countries where the product is registered. However, if there are important differences reflecting exposure of different types of patients to the drug, this information should be given. In case of serious differences in newly reported safety information concerning different forms of usage, this information shall be very important.

Due to the facilitation of the inspection, it will be more suitable to present usage information in different countries (indication, dosage, form, method of application, age group, special population, etc) in a table.

Country records should be listed in chronological order.

### 9.3.3 Updating the safety transactions conducted by the administrative authority or the registration holder

In this part, details on the types of safety transactions below, conducted in the reporting term, and in the period between data lock point and presentation of the report should be given:

- Suspension or cancellation of the registration,
- Non-renewal of the registration,
- Restrictions on distribution,
- Discontinuing clinical studies,
- Changes in dosage,
- Changes in the target group or indications,
- Changes in formulation,
- Urgent safety restrictions.

Safety reasons leading to these transactions should be defined, and relevant documents enclosed; all kinds of correspondence with health professionals stemming from such transactions (for instance, all *Dear Doctor* letters should be explained and their copies enclosed)).

### 9.3.4 Modifications in the reference safety information

The CCDS including the CCSI valid at the beginning of the report term should be used as reference. The table should be assigned a number and date, and enclosed to the PSUR. The most recent revision date should also be mentioned.

New changes made in the CCSI during the reporting term, such as counter-indications, warnings and measures, adverse reactions and interactions should be clearly defined, and a presentation concerning the changed parts be made. In the next report and the next reporting period, the revised CCSI should be used.

Except in urgent situations, including the designed modifications in product information material given to physicians, dentists, pharmacists, and consumers (including the patient guidelines) may take some time. Therefore, within the said period, there may be more "listed" information in the changed reference document (CCDS) compared to those in many other countries.

In case of serious differences among the information given in CCSI and SPC (or between official data tables/product characteristics documents approved in a country); the registration holder should prepare a short commentary on local differences and the consequences of these local differences on general safety evaluation, as well as suggested and implemented transactions. This summary commentary should be added to the application document enclosed to the PSUR, or included among the other appendices in the local presentation of the PSUR.

### 9.3.5 Patients' use of drugs

Basic information, detailed explanation, and examples concerning patient drug use are included in the CIOMS V report.

If possible, estimations about the patient's period of drug use should include the same period as the safety information in between. Even though the drug usage data are based on information collected in a period which does not completely include the period covered by the PSUR, the registration holder may make estimations based on available data. When such an estimation is made, it should be clearly explained which data are used, and why estimating for the PSUR period is reasonable (*for instance; long-lasting stable illness, seasonal use of drug,...*).

Registration holder should always use the same method of calculation in the PSURs belonging to the same product. If a change in this method is needed, in the first report including the change, previous (changed) and current method and calculations should be presented.

Instead of figure estimation, other usage data such as the no. of patient days, no. of prescriptions or number of dosage units is also deemed suitable; in such a case, the method used should be explained.

In bridge summary reports, when each PSUR period overlaps with another, it may be more appropriate to recalculate the patient drug use data in a way as to include the whole period of the report.

In order to arrive at patient drug use estimations, the Defined Daily Dosage (DDD) concept may be used. If possible and applicable, the data should be presented by differentiating according to sex and age (particularly for pediatric and adult patients).

In case of a group of reports indicating a potential problem, details should be given on a country basis if existing (*together with the locally recommended daily dosage*), or based on other differentiating characteristics.

### 9.3.6 Event presentations

In this part of the PSUR, because it will not be practical to present all adverse events one by one, the criteria used in selecting the events presented should be explained shortly.

This part should contain the explanation and analysis of selected adverse events including fatality, as well as new and relevant drug safety information collected under medical headings or system organ categories.

#### 9.3.6.1 General topics

Follow-up information concerning the events included in the PSUR may be collected later. If such an information is related to the interpretation of the event (for instance, if it has an important role in the definition or analysis of the event), it's necessary to include the new information in the subsequent PSUR and indicate correction or clarification in the previous event definition.

Registration holders are expected to follow the standard, recognized medical and scientific publications for safety information concerning their own products, and/or to avail themselves of one or more literature search/summarize services.

Care should be given to convey such events only once. Furthermore, whatever the "main source" in an event may be, if there is a literature, it should be denoted, and referred to.

Spontaneous reports coming from consumers or professionals other than health professionals, and that are not medically confirmed should, only if requested by the Pharmaceutical General Directorate, be presented as additional ranking lists and/or summary tables. Still, such reports should not be expected to be analyzed within the PSUR.

#### 9.3.6.2 Events presented as Ranking Lists

The types of events below should be included in the ranking lists:

- All serious adverse reactions and non-serious unlisted adverse reactions collected from spontaneous notifications
- All serious adverse reactions (that have been connected to the medicinal drug by the researcher or sponsor) collected from studies, or through the humanitarian program on early access to drugs
- All serious effects and non-serious unlisted effects collected from literature
- All serious effects collected from administrative authorities

Spontaneously reported, non-serious, listed adverse reactions should be presented as an appendix to the PSUR in the form of an ranking list, only when requested by the Pharmaceutical General Directorate.

Duplication must be prevented in events collected from literature and administrative sources.

#### 9.3.6.3 Presentation of Ranking Lists

The ranking lists should include each patient only once; no matter how many adverse reaction terms are reported for the event (See Annex 3, Table 3.3). If there are more than one adverse reactions, each should be mentioned, but the event should be listed under the most serious adverse reaction (finding, symptom, or diagnosis) to be determined by the registration holder.

The same patient may be experiencing different adverse reactions at different times (for instance, on different weeks during the clinical study). These experiences should be processed in separate reports. In this case, the same patient may be indicated in more than one ranking; where possible, reference should be made to them in the ranking list. The events should be presented in the form of a chart arranged in accordance with the standard organ system classification scheme.

When presenting common PSURs pertaining to co-marketed products, the name of the active substance/medicinal product should be presented in the version reported by the first reporter.

The following titles should generally be included into the ranking lists (See Annex 3, Table 3.3):

- Case reference number of the registration holder
- Country where the event has occurred
- Resource *(for instance, clinical research, literature, spontaneous, administrative authority)*
- Age and gender
- Daily dosage, pharmaceutical form, route of administration of the suspected medicinal product
- Date of commencement of the adverse reaction *(If not available, the best estimated date for the commencement as of the beginning of treatment).*
- Treatment dates. (If not available, estimated treatment period)
- The definition of the adverse reaction as reported and (where available) as interpreted by the registration holder *(The Turkish version should be available). (See section 9.2.5.2 for details).*
- The result of the adverse reaction on a case basis (for instance, recovered, fatal, recovering, sequeal, unknown). In multiple adverse reactions, the most severe among various results should be used and the consequences of adverse reactions in terms of the patient should be indicated.
- Relevant comments where available *(for instance, causality evaluation if the registration holder does not agree with the reported; concomitant drugs suspected to play a direct role in adverse reactions or to play a role through interaction; indication treated with suspected medicinal product(s); where available, the elimination of the interference/results of re-interference).*

It use of more than one ranking list may be useful or practical for instance for different dosage forms or indications, if this facilitates the presentation and the interpretation of difference days in relation with the product or conditions.

#### 9.3.6.4 Summary Charts

Normally, a total summary should be presented for each ranking list. It may be useful to use severe and non-severe adverse reactions and listed and non-listed adverse reactions or other distinguishing characteristics such as the source of the report. *(See Annex 3, Table 3.2 for the sample data presentation on severe effects).*

With regard to non-severe, listed, spontaneous reported effects, a summary chart should be drafted only where necessary *(see subsection 9.3.6.2).*

The terms used in these charts should be the terms used by the registration holder when defining the event *(see subsection 9.2.5.2).*

Besides for the cases received from administrative authorities, the data pertaining to the severe effects obtained from other resources *(see subsection 9.2.5.1.iv.)* should be presented only in a summary chart. Where deemed useful, the charts may be ranked in terms of source of information or country, for instance.

If the number of events is very little or information is inadequate for charts, an explanatory definition instead of a table is sufficient.

Data in the summary tables, just like the ordering lists that are their source, should be period data. However, in adverse effects that are both serious and unlisted, cumulative figures (for ex. all events reported until that date) should be included in the table(s) or enclosed as an explanatory note.

#### 9.3.6.5 Individual event story analyses carried out by the registration holder

This part may be used in stating short commentaries on the data concerning individual events. For instance, an opinion on specific serious or unexpected findings *(structure, significance, mechanism, reporting frequency, etc.)* should be given here. The emphasis here should be about individual event discussion; and it should not be confused with the general safety evaluation (See subsection. 9.3.9).

### 9.3.7 Studies

All uncompleted studies that reveal safety information (clinical, non-clinical, and epidemiological) with potential effect on product characteristics, specially planned or ongoing studies, and published studies concerning safety issues should be discussed in this part.

#### 9.3.7.1 Newly analyzed studies

Studies containing important safety information, and stemming from epidemiological, toxicological, or laboratory research newly analyzed in the reporting period should be explained. Method of study and results should be presented in an open and concise manner, paying attention to the usual data analysis and definition standards applied in clinical and non-clinical study reports. Copies of reports should be added only when deemed necessary.

#### 9.3.7.2 Targeted new safety studies

New studies that are planned and continued specially to analyze a real or assumed safety issue should be completed (for instance, objective, starting date, anticipated completion date, number of objects, summary protocol).

When possible and applicable, if temporary analysis is included in the study plan, intermediary results concerning ongoing studies should also be presented. When the study is completed and analyzed, final results should be presented in the subsequent PSUR, as explained in subsection. 9.3.7.1.

#### 9.3.7.3 Published studies

All reports and abstracts containing important safety findings and present in scientific and medical literature should be summarized with reference to their sources.

### 9.3.8 Other information

#### 9.3.8.1 Information on effectiveness

Ineffectiveness information concerning a product used for the treatment of serious or life-threatening illnesses should be defined and explained.

#### 9.3.8.2 Last minute information

All kinds of important and new information obtained after database being frozen for reporting may be presented in this part. For instance, important new events or important follow-up data are among these. These new data are required to be considered in the general safety evaluation.

### 9.3.9 General safety evaluation

The registration holder, considering last-minute information (*See subsection 9.3.8.2*), should present a short analysis of the data presented, and his own evaluation on the importance of the data collected within the term.

- A change in the characteristics of the adverse effects listed (*for instance, violence, termination, target group, etc.*)
- Serious unlisted adverse effects in the light of cumulative reports
- Non-serious, unlisted adverse effects
- Comments on whether an increase in reporting frequency of listed adverse effects and data indicate a serious change in adverse effect formation.

At the same time, the report should specify all kinds of new safety issues (*if there's no new information, then their nonexistence*) concerning the subjects below:

- Drug interactions
- Overdosage experiences and treatment
- Drug abuse and misuse
- Positive or negative experiences during pregnancy
- Experiences of special patient groups (for instance, children, the elderly, organ failure)
- Effect of long-term treatments

The general safety evaluation containing the points above should preferably be presented in Turkish.

### 9.3.10 Risk Management

#### 9.3.10.1 Risk Management Program

If the registration holder is implementing a product-specific risk management program, he can explain that program in this part.

9.3.10.2 Other risk benefit analysis reports

Apart from the PSUR, a comprehensive drug safety and risk/benefit analysis summary (*for instance, all indications being reviewed*) should be included in this part.

### 9.3.11 Conclusion

- Should specify which safety information is not compatible with previous cumulative experiences and reference safety information (CCSI);
- Should specify and explain suggested or implemented transactions

Upon making the decision to change the SPC, the registration holder should submit the variation application simultaneously with the PSUR and whenever this is not possible, should present a timetable for the application.

### 9.4 Contents of the PSUR bridge summary report

The summary report should not duplicate the information present in the PSUR. If necessary, the applicant should refer to the related parts of the relevant PSURs. Format of the bridge summary report should be similar to the usual PSUR format, but the content should be a review and summary of the cumulative information in the PSURs enclosed. The bridge summary report should include the following:

1. Estimated number of patients exposed to the drug in the period covered
2. Cumulative summary charts arranged according to organ category, severity, and being listed
3. A general summary of safety issues that have emerged during the period, solved, or still pending.

## SECTION V

## Post-Registration Safety Studies

### 10. Company Sponsored Post-Registration Safety Studies

### 10.1 Scope

This part includes all company sponsored studies carried out to evaluate the safety of registered drugs. These include cases where the drug has been supplied by the sponsor company, and where the drug has been normally prescribed in general practice or hospital environment.

Various data collection methods may be used to evaluate safety of registered drugs. As the necessity to shape the method used in accordance with certain products or risks is known, this guide defines basic principles to be applied in very different situations. Study methods in this field are still being developed, and therefore the formulations in this part shall be reviewed again to reflect developments in product safety evaluation.

This part concerns studies where a known safety issue is being investigated, and/or where the number of patients included in the study is to make a significant contribution to the relevant safety information concerning the product(s). While a study on a registered product is being conducted, a risk that is normally outside the scope of this guide may unexpectedly be determined. In this case, the registration holder and the Product Safety Authority should immediately inform the Pharmaceutical General Directorate, and both in intermediate terms and at the end of the study, should submit a short report on the proceedings.

Research conducted after a product is launched; for instance, clinical studies researching new indications, new methods of application, or new combinations are accepted as research on new medicinal products; and are not within the scope of the guide in this part.

In order not to cause any doubts as to a study being within the scope of the guide in this part or not, the company should discuss the designed protocol with the Ministry. In this subject, working principles stated by the Ministry should be followed meticulously.

## 10.2 Scope and Objectives of Post-Registration Safety Studies

Post-registration studies may be realized with the aim of determining previously unknown safety issues (forming a hypothesis), investigating potential risks (testing the hypothesis to prove a causality connection), or approving the expected safety profile of a product under marketing conditions. These studies may also be conducted to assess specified adverse effects, or determine the risk factors.

Under the following conditions, such studies are considered appropriate:

- For a drug with an unusual chemical structure or effect mechanism,
- If there's an uncertainty about the clinical connection of a toxic effect on animals,
- If there's an uncertainty about the safety profile,
- If there's a need to assess the adverse effects determined in clinical studies better, and to explain the risk factors,
- If there's a very specific use that should be monitored by a specialist.

The most suitable method here may be one of several modes of study including cohort studies based on observation, event supervision or event control studies. In the evaluation of safety of registered products, clinical studies (for instance, randomization) may also be used. Such clinical studies should be conducted in accordance with regulations.

The working arrangements to be used depend on the objectives of the study. These objectives should clearly be specified in the study protocol. All kinds of safety issues to be investigated should be specified in the protocol, and these subjects should be the aim of the recommended methods.

## 10.3 Study Types

### 10.3.1 Observational cohort studies

Patients should not be subscribed any drugs apart from those that may be used in normal medical practice. In order for a study to be accepted as based on observation, there should be no restrictions on the physician, or any influence on normal clinical practices.

Population studies should represent the general user population as much as possible, and in accordance with the objectives of the study, except for cases where there's a special target population (for instance a study concerning the elderly), it should not be selected specifically. Exclusion criteria should be limited to the counter-indications determined in the

SPC. In subsequent studies following these transactions, SPC on all products used should be given to participating physicians.

Observational cohort studies should normally include a suitable comparative group/groups. The comparative group(s) shall include patients with illness/indication(s) that is/are the object of study, and these patients shall generally be treated with alternative drugs or methods.

The decision to prescribe a product should clearly be distinguished from the decision to include that patient in the study. The reason for using the drug must be entered by the prescribing physician into the patient records among study documents.

Minimum and maximum number of patients that may be included by a single physician should be specified in the protocol.

### 10.3.2 Case control studies

Case control studies are generally conducted retrospectively. Comparison is made among cases where the investigated illness/event is present and exposed to the drug; and suitable control groups. The study should be designed considering factors such as bias that may affect the scientific results of the study.

### 10.3.3 Case supervision

The aim of case supervision is to investigate patients with illnesses, some of which may be related to the product. The registration holders sponsoring such studies should be in close communication particularly with relevant administrative authorities, to determine the most suitable arrangements for reporting the events.

### 10.3.4 Clinical studies

Sometimes, in order to explain adverse effect mechanisms and determine directions of measures, special (for instance, pharmacokinetic, pharmacodynamic or pharmacogenetic) clinical studies have to be conducted. Comprehensive clinical studies may also be beneficial in researching post-registration safety issues. In these types of studies, randomizing may be possible, but from other standpoints, it's necessary to try and investigate the patients under as normal conditions as possible. Exclusion criteria, if not particularly relevant to the objectives of the study, should be limited to the counter-indications specified in the SPC. Clinical studies should be in accordance with the principles of GCP (Good Clinical Practice). Post-registration studies that have initiative clinical research specifications should be realized in accordance with relevant regulations.

## 10.4 Relations with the Pharmaceutical General Directorate

Registration holders suggesting post-registration studies should discuss the draft protocol at an early phase with the Pharmaceutical General Directorate, and independent experts.

Special safety issues that may require investigation must be particularly noted. Relevant national legal requirements, regulations, and guidelines should be considered.

Before the study begins, a protocol should be made specifying its objectives and targets (including the explanation for statistical analysis and sample size), methods to be used, and records to be kept. The registration holder should present the Pharmaceutical General Directorate the protocol and recommended physician correspondence at least a month before the date planned for the beginning of the study. The responsibility for conducting the study should belong to the sponsoring drug company.

The registration holder should notify the beginning of the study, and normally within six months, or as the authorities demand, should present a short report on the development of the study.

In cohort studies, the development reports to be presented to the Ministry should, at the minimum, contain the following information:

- Number of patients determined in accordance with the study, charts on patients accepted and monitored,
- Total exposure estimate of the product to be studied, on a patient-year or month or day basis,
- Condition of all patients completing the study (for instance, in treatment/treatment ended, deceased, not monitored)
- Chart showing the reasons why treatment was abandoned during study,
- Table of all serious adverse events (digital and also as a ranking list).

If there are more than one product studied, the data should be reported separately for each product.

In general, only the data listed above must be included. The Pharmaceutical General Directorate may require additional information after reviewing the report.

Usual administrative requirements on reporting suspicious adverse effects should be met. Registration holders should ensure notification of serious suspicious adverse effects to themselves, and latest within fifteen days of this notification, should report these effects to the relevant department (Department of Clinical Studies for Clinical Studies, Department of Observational Studies for Observational Studies). Those events that were not suspected to be an adverse effect by the researcher, and non-serious adverse effects and events should not be reported one-by-one, but summarized in the final report. Reports on serious adverse effects surfacing during post-registration studies should be included in the PSUR. The Officer Responsible for the Safety of Products for Human Medicinal Use should notify TÜFAM of all other information on the medicinal product's benefit/risk evaluation, including post-registration safety studies.

The final report of the study should be sent to the Pharmaceutical General Directorate within 3 months after the study has been completed. This should preferably be a full report; however, within 3 months after the study ends a short preliminary report, and then within the next six months submission of the full report is also acceptable. Registration holders should prepare the contents of the report in accordance with *Good Clinical Practice* guidelines.

It may be necessary to conduct certain adaptations in accordance with specific requirements of the studies.

### 10.5 Promotion of drugs

Post-registration studies should not be planned and conducted to promote the use of drugs.

Company representatives should not participate in operations that can be deemed promotional activities.

### 10.6 Physician participation

Depending upon the work conditions of the physician, a payment within the framework of a nationally accepted wage scale may be offered to the physician for the extra time spent and expenses incurred.

No incentive in a scale as to influence the decision of participation in a post-registration study may be offered, demanded or given to a physician.

### 10.7 Ethical matters

Highest possible professional implementation and confidentiality standards should be ensured and national laws on data should be observed. Patient's right of confidentiality is the most important issue. Patient identity should not be disclosed in the study documents; and only authorized persons should be able to access identifiable personal details in case data confirmation procedure requires identification of these details. Identifiable personal details should always be kept confidential. (See *Good Clinical Practice* guidelines).

Responsibility of finding the information from personal medical records belongs to the medical authority (authorities) responsible for the patient. Such information should be directed to the medical executive appointed by the sponsor, and responsible for the use of such information thereafter.

## SECTION VI
## Evaluation

### 11. Pharmacovigilance Evaluation Pursued in the Post-Registration Period

The issuance of registration to a medicinal product indicates that, in the light of the information available at the date the document is issued, the product has a satisfactory benefit/risk ratio within the conditions defined in the SPC.

After being registered, the product shall be used in an environment different from that of clinical studies, and by a much greater group of people. More information that can influence the product's benefit/risk ratio shall surface. Evaluation of this information is a continuous process both for the drug companies, and for the administrative authorities.

Both the registration holders, and the administrative authorities should follow up all relevant information to execute their responsibilities below:

- To ensure that the necessary process is conducted in the face of new evidence influencing the benefit/risk ratio
- To inform medical professionals and patients by direct communication, about any changes in the registered product.

When new or changing information is collected that may influence the benefit/risk ratio of a medicinal product, the registration holder should forthwith inform the Pharmaceutical General Directorate.

### 11.1 Principles of Benefit/risk evaluation

Total benefit/risk evaluation should consider all the benefits and risks specified below, and balance them. Benefit/risk evaluation should be done separately for all indications that may influence the results and procedures to be done.

#### 11.1.1 Benefit evaluation

When a new or changing risk emerges, it is very important to re-evaluate the benefit of the medicinal product by using all current data. The benefit of a medicinal product might be seen as a decrease in the intensity of the illness as a result of that product's use. The benefit consists of three parameters:

(1) How much the medicinal product treats or cures the illness, or alleviates the symptoms
(2) Rate of responders
(3) Period of responding to the treatment

All kinds of present information that may influence the evaluation of the product's benefits, on misuse or the level of compliance in clinical studies should be noted. Quality of different evidences of benefit should be considered. Effectiveness and benefits should, as much as possible, be expressed quantitatively in a way that is comparable with the risks.

#### 11.1.2 Risk evaluation

Risk evaluation includes a progressive process requiring determining, confirming (including specifying the risk determinants), specifying the characteristics, and digitalizing the product safety risks in the group using the product. Total evaluation of the risk should consider all relevant information, including those below:

- National and international spontaneous adverse effect reports,
- Adverse effect data collected from observational and experimental clinical studies sponsored or not sponsored by the company,
- In vitro and in vivo laboratory experiments,
- Worldwide scientific literature,
- Congenital anomalies/records on birth defects,
- Research on pharmaceutical quality,

- Data on sales and product use.

When potential safety risks are determined that may influence the total benefit/risk ratio of the product or that have the possibility of interaction, the registration holder must recommend suitable studies. These studies should analyze in detail the structure and occurrence frequency of the said risks, on the condition of not constituting an unacceptable risk for the patients analyzed.

The important issued to be specified in risk evaluation are the following:
- Causality association evidences
- Severity
- Absolute and relative frequency,
- Presence of risk factors that may ensure taking protective measures.

Natures of different risk types should be considered.

### 11.1.3 Benefit/risk evaluation

If possible, both benefits and risks should be evaluated in absolute terms, and comparatively among different treatments. Evaluation of the degree of risk as acceptable depends on the seriousness of the illness treated. For instance;

- In treatment of an illness with a high degree of fatality, if it can be proven that there are more benefits to the treatment, serious adverse effect risk being high can be tolerated.
- For drugs used for chronic diseases or in treatment of incapacitating diseases, if there's a significant improvement in the quality of life or the prognosis, the risk can be tolerated up to a certain degree.
- In cases when the basic benefit is to alleviate symptoms of insignificant illnesses of healthy individuals; or when individuals are being treated not only for their own good, but also for the good of the community (for instance, vaccinations) safety standards should be very high.

## 11.2 Developing the benefit/risk ratio

The registration holder should try for the product to have as high a benefit-risk ratio as possible; and in the group being treated, the adverse effects of a medicinal product not to be more than its benefits. The benefit/risk profile of a medicinal product cannot be evaluated by itself; it should be compared with other treatments of the same illness.

The benefit/risk ratio can be improved by increasing the benefits, or by decreasing the risks through minimizing the risk factors (for instance, particularly by restricting use in patients under risk, decreasing the dosage, applying pre-treatment tests to determine patients under risk, and closely monitoring during treatment to enable early diagnosis of revocable dangers). While suggesting measures to improve the benefit/risk ratio of a product (for instance, in a patient group to whom it will possibly be beneficial, or by restricting drug use where there's no other alternative) feasibility of these measures under normal conditions of use should be considered.

Some measures within this context are listed below:

1. Changing the registration on indications, dosage recommendations, counter-indications, warnings or adverse effects, and consequently;
   -Changing the SPC and the patient guidelines to make them compatible with the registration;
   - Changing the promotion materials.
2. Direct communication of important safety information to medical professionals (*for instance, by letter and/or newsletter*)

When new and important safety issues emerge, registration holders should take new and urgent safety measures (*restrictions*) to meet the risk. These measures must immediately be discusses with TÜFAM. When, following a valid application, no objection is heard from the authorities, urgent safety measures may be announced, and the variation on the subject submitted to İEGM without delay. The urgent safety measure might also be started by the Pharmaceutical General Directorate Application for variation should be made latest by 15 days after the safety restrictions begin.

If there's a significant variation in the safety information in SPC, relevant health professionals must immediately be informed and the new SPC given. The patient guidelines handbook should also be updated and offered for use along with the product.

**11.3 Recalling a product from the market due to benefit/risk reasons**

In the event of the withdrawal of a product due to any reason in any part of the world, the Pharmaceutical General Directorate should forthwith be informed about the planned transaction.

In case the total benefit/risk ratio is regarded as unacceptable, the registration of the relevant medicinal product should forthwith be recalled and the Pharmaceutical General Directorate should forthwith be notified.

This transaction may be conducted voluntarily by the registration holders. The Pharmaceutical General Directorate should be notified significantly in advance about the planned transaction.

In case it is determined that the product is harmful in regular usage conditions, the Pharmaceutical General Directorate may suspend the registration or annul it for the purpose of safeguarding public health.

**11.4 Communication**

The content of public announcements, the letters written to healthcare professionals and the other letters sent from the registration holders to healthcare professionals, patients and the public should always be decided together with the Pharmaceutical General Directorate and the time schedule with regard to the distribution of this correspondence should be designated with the relevant authorized units. The procedure for the distribution of information should prevent the information from being communicated to the Pharmaceutical General Directorate later than to healthcare professionals, patients and the public.

# ADVERSE REACTION REPORT FORM
## Turkish Pharmacovigilance Center

| 1. Patient Initials | 2. Age | 2a. Date of Birth | 3. Sex | 4. Height cm. | 5. Weight: __kg. | 2. Severity Criteria |
|---|---|---|---|---|---|---|
| | | Day/Month/Year | Female<br>Male | | | Check the suitable box<br>Death<br>Day/Month/Year |

| B. ADVERSE REACTION(S) | | | | |
|---|---|---|---|---|
| 1. Describe the Adverse reaction | Reaction Onset (Day/Month/Year | Ending Date | Result | |
| | | | Recovered/Healed<br>Recovering/Healing | Life Threatening<br>Caused Hospitalization and/Or Prolonged Hospitalization Period (..days) |
| | | | Recovered/Healed with Sequeal<br>Continues<br>Terminated with death | Caused Permanent or Significant Disability or Incapacity<br>Congenital Anomaly and/or Birth Defect<br>Other |
| | | | Unknown<br>Other | Reason for death if the patient has died |
| | | | | Has autopsy been conducted?<br>Yes No<br>(If yes, attach the relevant document) |

3. Laboratory Findings (With dates – Day/Month/Year)

4. Relevant Medical Story/Concomitant diseases: (For instance: Allergy, pregnancy, consumption of cigarettes and alcohol, hepatic/renal impairment, diabetes, hypertension, etc.) With regard to congenital anomalies, please indicate all drugs taken by the mother at pregnancy, exposed diseases and last month of period. (Day/Month/Year).

| 1. Name of suspected drug | 2. Route of Administration | 3. Daily Dosage | 4. Date for starting medication (day/month/year) | 5.Date of quitting the Drug (day/month/year) | 6. Indication | 7. Has the drug been quitted? | 8. Have adverse reactions decreased when quitting the drug or lowering the dosage? | 9. Has the drug been re-administered? | 10. Have the adverse reactions re-occurred when re-administering the drug? |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Yes No Unknown | Yes No Unknown | Yes No Unknown | Yes No Unknown |
| | | | | | | Yes No Unknown | Yes No Unknown | Yes No Unknown | Yes No Unknown |
| | | | | | | Yes No Unknown | Yes No Unknown | Yes No Unknown | Yes No Unknown |

11. Concomitant Drug(s) (Except for Those Used in the Treatment of the Adverse reaction)

| | | | | | | 12.Other Observations and Comments: (In case of a Problem related with the quality of the Medicinal Product for Human Use, Please indicate the Batch Number of the Suspected Product, its Expiration Date and the Relevant Problem) |
|---|---|---|---|---|---|---|
| | | | | | | |

13. Adverse reaction: (Together with the drugs used for treatment and the date of usage (day/month/year))

D. INFORMATION PERTAINING TO REPORTING PERSONS

E. INFORMATION PERTAINING TO REGISTRATION/PERMIT HOLDER (To be filled only in case of reports submitted by the registration/permit holder:
Name, surname and contact information of Drug Safety Officer

| 1. Name, Surname: | 2. Profession: | 1. Name of Registration/Permit Holder: | |
|---|---|---|---|
| 4. Address | 3. Tel No: | | |
| 4. Address: | 5. Fax: | 2. Tel. No: | 3. Fax: |
| 4. | 6. E-mail: | 4. Address of Registration/Permit Holder: | 5. Type of Report: |
| 7. Signature: | 8. Has the report also been notified to the company?<br>Yes No | | Initial Follow-Up |
| 9. Date of Report: | 10. Type of Report:<br>First Follow-Up | 6. Report Number of Registration/Permit Holder: | 7. Source of Report:<br>Foreign Consumer<br>Observational Study<br>Literature |
| | 11. Medical Record No: | 8. Date of First Notification of the Registration/Permit Holder | Healthcare professional<br>a) Physician b) Pharmacist c) Dentist D) Nurse |
| | | 9. Date of this Report: | Institute Other than the Institute<br>Registration holder Others |

e-mail: TUFAM@saglik.gov.tr fax: 0312 309 71 18 tel: 0312 309 53 97 Please complete the form as accurately as possible. You may attach a page to the form.
Annex 2: CIOMS Form

| SUSPECT ADVERSE REACTION REPORT | |
|---|---|
| | |
| | |

I. REACTION INFORMATION

| 1. PATIENT INITIALS 2. (first, last) | 1a. COUNTRY | 2. DATE OF BIRTH | 2a. AGE | 3. SEX | 4-6. REACTION ONSET | 8-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION |
|---|---|---|---|---|---|---|
| 7-13. DESCRIBE REACTION(S) including relevant tests/lab data) | | | | | | PATIENT DIED<br><br>INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION<br><br>INVOLVED PERSISTENCE OR SGNIFICANT DISABILITY OR INCAPACITY<br><br>LIFE THREATENING |

## II. SUSPECT DRUG(S) INFORMATION

| 14. SUSPECT DRUG(S) include generic name) | | 20. DID REACTION ABATE AFTER STOPPING DRUG? YES NO NA |
|---|---|---|
| 15. DAILY DOSE(S) | 16. ROUTE(S) OF ADMINISTRATION | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? YES NO NA |
| 17. INDICATION(S) FOR USE | | |
| 18. THERAPY DATES (from/to) | 19. THERAPY DURATION | |

III. CONCOMITANT DRUGS AND HISTORY

| 22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction) |
|---|

| 23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergies, pregnancy with last month of period, etc.) |
|---|

| 24a. NAME AND ADDRESS OF MANUFACTURER | | |
|---|---|---|
| | 24b. MFR CONTROL NO. | |
| 24c. DATE RECEIVED BY MANUFACTURER | 24d. REPORT SOURCE<br>STUDY LITERATURE<br>HEALTH PROFESSIONAL | |
| DATE OF THIS REPORT | 25a. REPORT TYPE<br>INITIAL FOLLOW-UP | |

Annex 3
Periodic Safety Update Reports
Tables 3.1-3.3.

Table 3.1:
Individual Presentation of Individual Case Stories
(See Subsection 1.4.3.6 for Detailed explanation)

| Source | Type of Case | Only Summary Chart | Ranking List and Summary Chart |
|---|---|---|---|
| 1. Reports Submitted Directly to the registration holders | S | - | + |
| | NS UL | - | + |
| - Spontaneous adverse reaction reports* | NS L** | + | - |
| | S R | - | + |
| - Studies and early drug access programs | | | |
| 2. Literature | S | - | + |
| | NS UL | - | + |
| 3. Other Sources | S | - | + |
| - Administrative authorities | | | |
| - Contracted partners | S | + | - |
| - Register records | | | |
| | | + | - |
| | S | | |

* Medically non-confirmed reports must be attached to the PSUR as a ranking list and/or special chart
** The ranking list should be attached to the PSUR only in case of demand from the Pharmaceutical General Directorate
S=Severe
L=Listed
R=Regarded to be related with the Researcher of the sponsor
NS=Non-severe (Not Severe)
UL=Unlisted

Table 3.2:

**Sample Special Chart****
**Number of Reports Obtained from Spontaneous (Medically Confirmed), Clinical Research and Literature Cases on a Term Basis (Findings, Symptoms and Diagnosis): All Severe Adverse Reactions**

*means unlisted adverse reactions.

| Body system/adverse reaction term | Spontaneous/Administrative authorities | Clinical Researches | Literature |
|---|---|---|---|
| CNS | 2 | 0 | 0 |
| Hallucinations* | | | |
| etc | | | |
| etc. | | | |
| Sub-total | | | |

| | | | |
|---|---|---|---|
| CV<br>Etc<br>Etc<br>Sub-total | | | |
| Etc | | | |
| TOTAL | | | |

The number of patients-cases represented with the tabulated terms should be indicated as a footnote(or elsewhere). (e.g : x-spontaneous/administrative, y-clinical research, z-literature cases)
** This table is only an example for various possible data presentations held by the right holding registration owner (e.g : severe and non-severe reactions may be indicated in the same or different tables, etc.)

Table 3.3:

Sample Ranking List

| REGISTRATION HOLDER NO | COUNTRY | SOURCE | AGE/GENDER | DAILY DOSAGE Mg/day | DATE OF COMMENCEMENT OF REACTION Or the period before the commencement of the reaction | TREATMENT DATES Or treatment period | DEFINITION OF THE REACTION | RESULT | COMMENT ON THE RESULT |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | |

**Annex 4**
**PSUR presentation template**

**<Batch no. > PERIODIC SAFETY UPDATE REPORT relevant**

**ACTIVE SUBSTANCE(S): <Name(s) >**
**ATC CODE(S): <Code(s) >**

**MEDICINAK PRODUCTS COVERED:**

| Name of medicinal Product | Registration Number | Registration Date<br>Indicate Date of Birty**= | Registration Holder |
|---|---|---|---|
| <> | <> | <> | <> |

**WORLD REGISTRATION DATE:** <Date>
**PERIOD COVERING THE REPORT:**
From-to (Data lock point)

**DATE OF THIS REPORT:**
Date

**VOLUME:** Number / Total number of volumes

OTHER INFORMATION:
<Other distinguishing or explanatory information, upon the of the registration holder>

**DATA LOCK POINT OF THE NEXT REPORT:**
<Date>
NAME AND ADDRESS OF REGISTRATION HOLDER:
<Name>
<Address>

NAME AND CONTACT INFORMATION OF THE OFFICER RESPONSIBLE FOR THE SAFETY OF THE MEDICINAL PRODUCT FOR HUMAN USE:
<Name>
<Address>
<Telephone number>
<Fax number>
<e-mail address>

SIGNATURE: <Signature>

## LIST OF BATCH NUMBERS

| <Batch numbers> | <period of coverage> |
|---|---|
| | |

## DISTRIBUTION LIST

| <Competent authority> | <Number of copies> |
|---|---|
| | |