ANNEX

GLOSSARY OF TERMS

*Adverse drug-event/adverse experience* Any untoward medical occurrence that may appear during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with the treatment.

*Adverse reaction* A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.

*Analyses of secular trends* Examine trends in disease events over time or across different geographical locations and correlate them with trends in putative exposures, such as rates of drug utilization. The unit of observation is a subgroup of a population rather than individuals.

*Analytic studies* Studies with control groups, namely case-control studies, cohort studies, and randomized clinical trials.

*Anticipated harmful effects* Unwanted effects of drugs that could have been predicted on the basis of existing knowledge.

*Association* When two events occur together more often than would be expected by chance.

*Attributable fraction* The proportion of the outcome (among those exposed to the factor) that can be attributed to exposure to the factor, taking into account the proportion of the outcome in those unexposed.

*Attribution* Process of deducing the causative role of the suspect drug/s in producing an adverse event.

*Bias* Any effect at any stage of investigation or inference tending to produce results that depart systematically from the true values.

*Case reports* Reports of the experience of single patients. In pharmacoepidemiology a case report describes a single patient exposed to a drug and who subsequently experienced a particular, usually adverse, outcome.

*Case series* Reports of collections of patients, all of whom have a common exposure, examining what their clinical outcomes were. Alternatively, reports of patients with a common disease examining their antecedent exposures. No control group is present.

*Causality* The relating of cause to the effect produced. A cause is termed "necessary" when the variable must always precede the event; "sufficient" if the variable inevitably initiates or produces the effect. Any given cause may be necessary, sufficient, neither or both.
**Certain drug causality** A clinical event, including laboratory test abnormalities, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

**Clinical pharmacology** The study of the effects of drugs in humans.

**Clustering** A closely grouped series of events or cases with well defined distribution patterns, in relation to time or place or both.

**Confounder** Variable other than the risk factor and outcome variable under study that is related independently both to the risk factor and to the outcome. A confounder can create an apparent association between the risk factor and the outcome or mask a real one.

**Cohort study** A study that identifies defined populations and follows them forward in time, examining their rates of disease. A cohort study generally identifies and compares exposed patients with unexposed patients or to patients who receive a different exposure.

**Conditional/unclassified drug causality** A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or the additional data are currently under examination.

**Criterion validity** The ability of an instrument to measure what it is supposed to measure, as judged by agreement with a gold standard.

**Cross-sectional** Studies which examine populations at one point in time.

**Descriptive studies** Studies that do not have control groups, namely case reports, case series, and analyses of secular trends. They contrast with analytic studies.

**Detection bias** An error in the results of a study due to systematic difference between the study groups in the procedures used for ascertainment, diagnosis, or verification of the disease.

**Determinant** Any factor that brings about change in a health condition, or other defined characteristic.

**Dose-response relationship** A relationship in which a change in amount, intensity, or duration of exposure is associated with a change in risk of a specified outcome.

**Drug utilization evaluation studies** Studies which assess the appropriateness of drug use. They are designed to detect and quantify the frequency of drug use problems.
**Effect modification**  Occurs when the magnitude of the effect of a drug in causing an outcome differs according to the level of a variable other than the drug or the outcome.

**Epidemiology**  Study of the distribution and determinants of diseases in populations.

**Experimental studies**  Studies in which the investigator controls the therapy that is received by each participant, generally using that control to randomly allocate patients among study groups.

**Face validity**  Judgement about validity of an instrument based on intuitive assessment of the extent to which the instrument meets a number of criteria including applicability, clarity and simplicity, likelihood of bias, comprehensiveness, and whether redundant items have been included.

**Hypothesis generating studies**  Studies that give rise to new questions about drug effects to be explored further in subsequent studies.

**Incidence rate**  Measure of the frequency of the disease or outcome. The number of new cases which develop over a defined time period in a defined population at risk, divided by the number of people in that population at risk.

**Information bias**  Error in the results of a study due to a systematic difference between study groups in the accuracy of the measurements being made of exposure or outcome.

**Life threatening**  The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it was more severe.

**Monitoring**  The performance and analysis of routine measurements aimed at detecting changes in the environment or health status of populations.

**Misclassification bias**  Error resulting from classifying study subjects exposed when they are unexposed, or vice versa. Alternatively, misclassification bias resulting from classifying study subjects with a specific disease outcome when they are truely not, or vice versa.

**Nonexperimental studies**  Studies in which the investigator does not control the therapy but observes and evaluates the results of ongoing medical care. The study designs that are used are those that do not involve random allocation, namely case reports, case series, analyses of secular trends, case-control studies, and cohort studies.

**Non-serious event**  Adverse event which does not compromise functional activity, is usually mildly incapacitating, and is not associated with death, hospitalization, prolongation of hospitalization, permanent or severe disability, or otherwise is not life-threatening.
**Observational studies**  Studies in which the investigator does not control the therapy, but observes and evaluates the results of ongoing medical care. The study designs that are used are those that do not involve random allocation, namely case reports, case series, analyses of secular trends, case-control studies, and cohort studies.

**One-group, post-only study design**  Consists of making only one observation on a single group which has already been exposed to treatment.

**Pharmacodynamics**  The study of the relationship between drug level and drug effect. It involves the study of the response of the target tissues in the body to a given concentration of drug.

**Pharmacoepidemiology**  The study of the use and effects of drugs in large numbers of people.

**Pharmacokinetics**  The study of the relationship between the dose of drug administered and the serum or blood level achieved. It deals with drug absorption, distribution, metabolism and excretion.

**Pharmacology**  The study of the effects of drugs.

**Pharmacovigilance**  The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.

**Possible drug causality**  A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

**Post-marketing surveillance**  The study of drug use and drug effects after marketing, which employs epidemiological methods characterised by their observational, rather than interventional, nature.

**Post-registration surveillance**  The study of drug use and drug effects after registration, which employs epidemiological methods characterised by their observational, rather than interventional, nature.

**Prevalence rate**  Measure of how common a disease or outcome is. The number of existing cases in a defined population at a given point in time or over a defined time period, divided by the number of people in that population.

**Prevalence study bias**  A selection bias, which may occur in studies when prevalent cases rather than new cases of a condition are selected for a study.

**Probable/likely drug causality**  A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.
**Prospective study**  Study performed simultaneously with the events under study.

**Prospective case report**  Drug exposure is defined in the case prior to knowledge of outcome.

**Protopathic bias**  Interpreting as a result of an exposure a variable that is in fact its determinant.

**Random allocation**  Assignment of subjects who are enrolled in a study into study groups in a manner determined by chance.

**Random error**  Error due to chance.

**Randomized clinical trials**  Studies in which the investigator controls the therapy that is to be received by each participant and uses that control to allocate patients among the study groups randomly.

**Recall bias**  Error in the results of a study due to a systematic difference between the study groups in the accuracy or completeness of their memory of their past exposures or health events.

**Retrospective study**  Study conducted after the events under study.

**Retrospective case report**  Drug exposure is defined in the case after knowledge of outcome.

**Risk**  The probability that an event will occur.

**Screening**  The presumptive identification of unrecognized disease or defect by the application of tests, examinations or other procedures which can be applied rapidly. Screening is an initial examination only and positive responders require a second diagnostic examination.

**Selection bias**  Error in a study that is due to systematic differences in characteristics between those who are selected for the study and those who are not.

**Sensitivity**  The proportion of persons truely having a characteristic who are correctly classified as having it.

**Serious reaction**  A “serious” reaction is defined by the ICH (International Conference on Harmonization) as any untoward medical occurrence that at any dose: (i) results in death, (ii) is life-threatening, (iii) requires patient hospitalisation or prolongation of existing hospitalisation, (iv) results in persistent or significant disability/incapacity, or (v) is a congenital anomaly/birth defect.

**Side effect**  Any unintended effect of a pharmaceutical product occurring at doses normally used in humans which is related to the pharmacological properties of the drug.
**Signal**  Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information.

**Specificity**  The ability of a method, system or tool to correctly classify the proportion of persons who truly do not have a characteristic, as not having it.

**Spontaneous reporting system**  System in which case reports of adverse events are voluntarily submitted from health professionals and pharmaceutical manufacturers. This system may serve as an early warning system for adverse events.

**Surveillance**  Ongoing scrutiny, generally using methods distinguished by their practicability, uniformity, and rapidity, rather than by complete accuracy. Its main purpose is to detect changes in trends or distribution in order to initiate investigative or control measures.

**Systematic error**  Error introduced into a study by its design rather than due to random variation.

**Type A reactions**  Adverse reactions which are a result of an exaggerated but otherwise usual pharmacological effect. These tend to be common, and dose-related, and predictable. They can usually be treated by reducing the dose of the drug.

**Type B reactions**  Adverse reactions which are aberrant, and may be due to hypersensitivity or immunologic reactions. These tend to be uncommon, not related to dose, and unpredictable. They usually require cessation of the drug.

**Unanticipated harmful effects**  Unwanted effects of drugs that could not have been predicted on the basis of existing knowledge.

**Unclassifiable drug causality**  A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

**Unexpected adverse reaction**  An adverse reaction, the nature or severity of which is not consistent with domestic labelling or market authorization, or expected from characteristics for the drug.

**Unlikely drug causality**  A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals, or underlying disease provide plausible explanations.