## COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

## NOTE FOR GUIDANCE ON THE EXPOSURE TO MEDICINAL PRODUCTS DURING PREGNANCY:

**NEED FOR POST-AUTHORISATION DATA**

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**Note:**

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NOTE FOR GUIDANCE ON THE EXPOSURE TO THE MEDICINAL PRODUCTS DURING PREGNANCY: NEED FOR POST-AUTHORISATION DATA

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These notes are intended to provide guidance on how to monitor accidental or intended exposure to medicinal products during pregnancy and specific requirements for reporting data and adverse outcomes of pregnancy exposure. The notes also include detailed recommendations regarding presentation of data collected on exposure in pregnant women.

The major objective of pharmacovigilance with regard to the exposure of pregnant women is to collect information on safety in pregnancy so that better information can be provided to health care practitioners and patients. Information on drug exposure in pregnancy is necessary to identify agents harmful to the developing fetus. In addition, data on pregnancy exposure can also establish that the fetal toxicity of a product is limited.

The notes also concern the use in men of medicinal products which might have effects on the fetus via semen because of their mutagenic or teratogenic potential (e.g. cytostatic drugs etc). The notes relate particularly to new products and to those "old" products for which reliable data in animals are lacking and experience in humans is poorly documented.

It should also be noted that this guideline will not cover the specific aspects of safety and efficacy of medicinal products licensed for pregnancy-related symptoms and disorders, because more adequate data from clinical trials and from Periodic Safety Update Reports (PSURs), as specified in Volume 9 of the Rules Governing Medicinal Products in the European Union, are already provided by the Marketing Authorisation Holder (MAH). Other products, for example, herbal medicines, and the use of medicinal product during breast-feeding are not covered in this guideline.

These notes should be read in conjunction with the Council Regulation (EEC) 2309/93 (Title II, Chapter 3), European Parliament and Council Directive 2001/83/EC (Title IX) and Commission Regulation (EC) 540/95, as well as in conjunction with other EU and ICH Guidance documents, especially:

- Volume 9 of the Rules Governing Medicinal Products in the European Union (Pharmacovigilance - Medicinal Products for Human Use)
- ICH topic E2C - Note for Guidance on Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs (CPMP/ICH/288/95, adopted in December 1996)
- Addendum to ICH topic E2C (CPMP/ICH/4679/02, adopted in February 2003)
- ICH topic E1A: The Extent of Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions (CPMP/ICH/375/95, adopted in November 1994)
• Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions (ENTR//F2/BL D (2003)-adopted in April 2003, Eudravigilance-CT Module)

• ICH E2E: Note for Guidance for Pharmacovigilance Planning (CPMP/ICH/5716/03 released for 6 months consultation in November 2003)

• ICH E2D: Note for Guidance on Post-Approval Safety Data Management: Definitions and Standards for expedited reporting (CPMP/ICH/3945/03, adopted in November 2003)

1. INTRODUCTION

During the development of a new medicinal product, the test product will be given to healthy individuals and to carefully selected patients. Unless the product is intended specifically for use during pregnancy, the clinical trial program almost never includes pregnant women despite the fact that some pharmacological treatments have to be continued during pregnancy. In most clinical study protocols, where women of childbearing age are included, effective contraception must be used. For this reason, virtually the only data available to evaluate reproductive risk when a new medicinal product is approved for marketing are from preclinical studies, which are not always predictive of human risk.

Consequently many medicinal products are subject to contraindications or special warnings in pregnancy because they have not been sufficiently studied during pregnancy or studies in animals have revealed adverse effects on the fetus (teratogenic, fetotoxic or other).

Use of medicines in pregnancy is not uncommon. It is recognised that many pregnancies are unplanned and some prescription and non-prescription medicinal products are frequently used by women of childbearing age, despite the fact that the benefits and risks are often unknown or poorly characterised.

Different studies have shown that there is a very wide range in the frequency of drug use during pregnancy among different countries

2. GENERAL CONSIDERATIONS REGARDING INFORMATION ON EXPOSURE IN PREGNANCY AND CRITERIA TO SELECT MEDICINAL PRODUCTS FOR WHICH THIS INFORMATION IS NECESSARY

2.1 Background

Most drugs or chemical substances administered to a pregnant woman could have effects on the fetus before the placenta is fully developed, but are subsequently also able to cross the placenta to at least some extent. Almost every substance used for therapeutic purposes in the mother has the potential to reach the fetus with the consequential potential for harmful effects, depending on whether the rate and extent of drug transfer results in sufficient concentrations within the fetus.

Drug use might have a different impact at different stages of pregnancy. The spectrum of effects varies according to the period of exposure. For example, the exposure to a teratogen during the period of organogenesis (days 15 to 60 post-fertilization) may induce major malformation, growth retardation or death whereas exposure during the second or third trimester may induce growth retardation, renal insufficiency, neurological disorders, stillbirth, etc.
Two important conclusions can be drawn from the above considerations:

In order to minimise the fetal risk of exposure, drug therapy of the mother should be restricted as much as possible. This principle, however, cannot be applied in all cases. The mother may have a serious illness which in itself requires treatment or an untreated condition may confer significant risk to the fetus.

In order to optimise the knowledge about any potential teratogenic or embryotoxic/fetotoxic drug effects and the doses and concentrations at which such effects will develop, it is desirable to gather information about all substances and drugs that are taken by pregnant women. At present, this approach does not seem to be realistic.

Drug treatment of the male prior to or around the time of conception and/or during pregnancy could affect the offspring due to a drug-induced defect in the spermatozoon itself such as an effect on the DNA or chromosome or due to an effect caused by the presence of the drug in the seminal fluid.

2.2 Criteria for assessing the need for information on drug exposure during pregnancy

It is good practice to try always to ascertain information on drug exposure in pregnancy. However, there are various situations where an assessment of the fetal effects following exposure of pregnant women to medicinal products is particularly important:

- Conditions and diseases where drug therapy is essential for maternal and/or fetal benefit and where discontinuation or omission of treatment would result in increased risk for the mother and/or the fetus.

In these situations, the potential harm imposed by drug therapy to the fetus must be weighed against the risk of lack of therapy both to the mother and the fetus. Examples of such conditions and diseases include asthma, autoimmune disorders, diabetes mellitus, epilepsy, high blood pressure, hyperthyroidism, infections, intoxications, malignant diseases, psychiatric disorders such as depression, schizophrenia or alcohol disease, thromboembolic events, as well as use of general anaesthetics, vaccines and treatments for prevention of transplant rejection.

There is a special need for information in situations when currently available treatment options are already severely limited due to known or suspected risks established from animal studies or human experience. Examples of these situations include: antiepileptic, antineoplastic and antithyroid agents. This statement must not, however, be equated with a waiver for other products, for which only limited or no information about their impact during pregnancy exists. The database established for collecting information on antiretroviral therapy is a good example of a solution to the problems of collecting information, which could be followed for other products.

- Conditions and symptoms where drug treatment, though not necessarily required, is frequently given, with or without prescription. This group mainly comprises treatment of common symptoms such as constipation, fatigue, fever, and mild to moderate forms of allergic symptoms, influenza-like infections, mood alterations, nausea/vomiting and pain.

Safety concerns emphasise the need for data collection on exposure during pregnancy and the importance of pregnancy databases in revealing potential teratogenic/embryofetotoxic signals. On the other hand, medicinal products, for which well-conducted epidemiological studies in pregnant women failed to demonstrate a risk to the fetus in the first trimester or in later trimesters, may be exempted.
• Treatment with drugs belonging to a class of substances or having a similar mechanism of action to:
  - Substances whose teratogenic, embryotoxic, fetotoxic or mutagenic effects in humans is suspected from case reports and animal studies
  - Substances whose potential for teratogenic or embryotoxic/fetotoxic or mutagenic effects in humans has already been established
    In these cases, it is of special importance to monitor any exposure to the drug before pregnancy was diagnosed or where appropriate contraceptive measures were either not taken or failed. There is an inherent overlap of drugs and substances addressed in this point with those used in the situations mentioned.
• Drugs representing a completely new chemical entity or exhibiting a new mode of action not already covered by the previous categories.

2.3 Specific recommendations for Medicinal Products for which information on exposure during pregnancy is essential

The medicinal products where there is a special need for surveillance during pregnancy are identified according to the above-mentioned criteria.

For those medications, the MAH should develop appropriate measures of active surveillance. The choice of the method of surveillance will depend on how frequently the drug is used, the type of adverse outcome to be monitored (e.g. birth defects, malignancy, psychomotor retardation) and the magnitude of the risk.

For new products, a summary of the potential risks of exposure in pregnancy and of the potential need for the product during pregnancy should be included in the Pharmacovigilance Specification provided by the MAH at the time of the licence application. This should lead the MAH to propose a Pharmacovigilance Plan in order to evaluate the potential risk of a product and/or to provide missing information on the safety of the product in pregnancy.

In general, exposure during the whole pregnancy should be monitored. For drugs with extended half-lives, data on exposure before the start of pregnancy should also be provided, with an appropriate time frame to be chosen according to the pharmacokinetics of the individual drugs.

3. IDENTIFICATION AND REVIEW OF ALL POTENTIAL SOURCES OF HUMAN PREGNANCY DATA

3.1 Pre-Authorisation Human Pregnancy Data

3.1.1 Clinical experience in pre-approval studies

In clinical trials which include female patients of reproductive age, there may be occasional inadvertent pregnancy exposure to the product. This inadvertent exposure is usually restricted to the early first trimester. This exposure could, however, provide opportunities for collecting data on the pharmacology and, to a lesser extent, efficacy and safety of drugs in pregnant women. Efforts should be made to collect data on the outcome for both mother and fetus/child should the pregnancy be continued.

For individuals who must have a medicine during pregnancy for treatment of an underlying disease and have been fully informed of the known benefits and risks, similar opportunities for conducting ‘phase I’ studies comparing blood levels in pregnant women in different trimesters
and in non-pregnant women receiving the same dose should be considered. Again there should be assiduous collection of data on the outcome for both mother and child.

Data from physiological studies, for example of hepatic and renal blood flow or CYP3A4 activity during pregnancy, may also predict changes in activation or clearance of specified products during pregnancy.

3.2 Post-Authorisation Human Pregnancy Data- Overview of current sources of information

3.2.1 Spontaneous reports / Case series

Spontaneous reports of pregnancy exposure are the most common source of post-approval data available on the safety of medicinal products in pregnancy.

Sources include databases of national regulatory authorities, national congenital anomaly registries, MAHs, and the National Association of Medical Examiner’s Pediatric Toxicology (PedTox registry (US)).

Data are often limited to spontaneous reports of adverse outcomes and may be biased. Even if the nature of spontaneous reports from pregnancies rarely permits determination of a causal link between a single product and an outcome, the occurrence of several reports of a distinct congenital abnormality associated with exposure may constitute a signal and a number of teratogens have been identified in this way. Existing systems for spontaneous reports of toxicity should, however, be optimised. Specific recommendations and requirements for reporting data and adverse outcomes of pregnancy exposure are provided in section 4 of this guidance.

It is also important to collect information on pregnancies which have a normal outcome. Not infrequently pregnant women or health care professionals will contact either a MAH or a local pharmacovigilance centre to request information on the teratogenic potential of a drug which has been taken either before the woman has realised she is pregnant or without realising the possible effects on the fetus. This is an ideal opportunity to collect data on exposure before the outcome of the pregnancy is known. Every effort should be made to contact the health care professional, who is caring for the woman, for outcome data after a suitable interval.

3.2.2 Registries

3.2.2.1 Birth defects registries

A population-based registry of children born with congenital malformations is one of available tools for the investigations of birth defects. This has been used for conducting case-control studies (see 3.2.3.6).

3.2.2.2 Pregnancy exposure registries

Prospective pregnancy exposure registries for screening and analysis have been used to identify and estimate risks associated with exposure to drugs. Registries may also be used to identify risk modifiers and to quantify longer-term effects. Possible sources for European registry studies include the Swedish Medical Birth Registry, a national population based registry, accumulating data on drug exposure during pregnancy for the whole pregnant population of Sweden (>90,000 per annum). Another similar, but smaller cohort database is the Danish Medical Birth Registry.
Registries may have very different foci, depending on whether they are set up and coordinated centrally by government agencies, such as the Swedish Medical Birth Registry, or by industry or academia. Thus, a registry can be organised to monitor a specific drug or to follow patients suffering from a specific medical condition or have a wider focus on a whole population. The accuracy of the registry information will be highly dependent on the access to case records of mother and neonate, i.e. both exposure and outcome data must be available.

3.2.3 Epidemiological studies

3.2.3.1 Randomised controlled trials (RCTs)

It is recognised that there are barriers to conducting RCTs in pregnant women. However, there are occasional reports of such studies in the published literature (e.g. asthma, HIV) and where the study is in the best interest of both mother and infant it may be feasible. Studies may also aim to prove a beneficial effect of a drug on the fetus. An example of this is studies on the use of folic acid in women around the time of conception to investigate potential preventive effects on the development of neural tube defects.

3.2.3.2 Cohort studies

There are several publications in the literature from cohort studies investigating effects of drugs in pregnant women. The advantage with a cohort study is that identification of patients before the outcome is known will minimise recall bias. Cohort studies need to be adequately controlled for underlying medical conditions, disease severity, multiple medications and demographic factors. Large sample sizes are required– particularly if the outcome of interest is rare.

3.2.3.3 Record linkage

For long-term ‘structural’ effects and some ‘non-structural’ - and therefore not immediately detectable – problems, registry data could be a source of information, provided that a registry containing exposure data could be linked with subsequent information collected later in life on those exposed individuals. If information is available from computerised medical files on a defined exposed group of individuals with unique identification numbers, the files can be cross-linked to other files, containing information on subsequent fate of those individuals.

Record linkage has been used to assess effects of parental alcohol and/or smoking habits or occupation on certain neonatal outcomes. In another example, a lack of association between intra-muscular administration of vitamin K to newborn infants and subsequent childhood cancer, an association that had been postulated in a previous smaller study, was demonstrated with high power, by linking the Swedish Medical Birth Registry to a cancer registry.

3.2.3.4 Uncontrolled observational studies

Very large uncontrolled observational studies with predefined outcomes, possibly using prescription tracking or named pharmacy sales records for non-prescription drugs may provide hypotheses/signals or reassurance.

3.2.3.5 Case control studies

These studies identify individuals with a specific outcome, e.g. a congenital malformation, and a control group and interview both groups as to exposure. In the case of specific malformations,
such studies often have sufficient statistical power but they are subject to various types of recall bias, which are difficult to control for. The Hungarian case control surveillance of congenital abnormalities, which also includes some prospectively collected data, includes data on more than 22,000 cases, 38,000 population controls and more than 800 patient controls with a specific genetic abnormality (Down Syndrome) and is the largest case control data set in the world and has been used for the analysis of more than 500 drugs.

### 3.2.3.6 Fetal therapy studies

Efficacy and safety information from studies with predefined outcomes, for example use of corticosteroids in mothers with preterm labour to induce fetal pulmonary maturation, should be collected. Outcome measures include fetal loss and infant mortality rates, gestational age at delivery, birth weight, premature rupture of membranes, neonatal complications, congenital malformations and developmental delay.

### 3.2.4 Other studies

#### 3.2.4.1 Pharmacokinetic studies

A number of studies in the published literature have addressed the pharmacokinetics (PK) of specific medicines in pregnancy, notably antibiotics, valaciclovir, theophylline, methadone, antiepileptics, nortriptyline and enoxaparin. Studies have particularly addressed the PK of agents where there is known to be a benefit from therapy, particularly addressing the late second and third trimesters and early postpartum period. Population PK studies have been suggested as a preliminary step prior to conducting more invasive intensive PK studies (or possibly as a replacement).

#### 3.2.4.2 Pharmacogenetic studies

It has been proposed that high maternal concentrations of both the active compound and poor elimination of toxic metabolites may be major determinants of malformations. Data on gene expression in pregnancy and metabolic variation may, in specific instances, help to predict effects and to identify individuals at a higher risk.

### 3.3 Data quality

#### 3.3.1 Exposure data

High levels of recruitment have been achieved using direct prospective enrolment of women, either specifically for pregnancy exposure studies or in addition to routine contact with a healthcare provider such as at antenatal care visits. All cohort studies, including those based on registries, should try to address exposure in specified time periods of the pregnancy. Information on timing, dose and duration should be recorded as accurately as possible.

Ideally, drugs should be studied individually as all members of a given drug class do not necessarily have the same potential for adverse effects on pregnancy and/or the fetal development.

#### 3.3.2 Outcome data

Adverse outcome data of fetal exposure encompass both ‘typical’ structural malformations, which are often – but not always – detected in the neonatal period and long-term functional or
non-structural (i.e. not easily detected in the immediate neonatal period) effects that can be potentially very important but also very difficult to detect or define. Some cardiac, renal and intestinal malformations are not always diagnosed immediately postpartum and, therefore, rates are significantly influenced by duration of follow-up and availability of diagnostic tests.

It is important to note that the recorded incidence of a certain malformation may be influenced by the degree of use of antenatal diagnosis and subsequent abortion. This is particularly important with the most severe malformations, for example anencephaly. Such outcome data may be difficult to retrieve, but should be sought. To detect an increase in anomalies incompatible with life, it is essential to collect information on autopsy results at stillbirth and, if possible, on examinations of the fetus after spontaneous or induced abortion. It is well recognised that review of birth certificates is not an accurate method of ascertaining pregnancy outcome as individuals who have not examined the neonate often complete the forms, whereas neonatal hospital records are more reliable. However, diagnoses may arise anew or be modified as the child is more thoroughly examined and undergoes additional testing. Involvement of mothers could minimise loss to follow-up. Registries involving examination by a group of professionals (ideally including a paediatrician) following a specific protocol and allowing for blinding to maternal exposure could generate more informative data also from a smaller number of patients, e.g. an epilepsy registry.

It is important to collect details of “normal” outcomes as this can not only provide reassurance but may also provide information on the critical exposure times when other outcomes have been abnormal.

### 3.3.3 Data standardisation

The validity of all information is dependent on the accuracy of diagnosis and recording. Information should include exact dates of exposure as accurately as possible (gestational length should be specified by method of assessment and expressed as weeks + days) as susceptible periods for specific malformations may be less than one week.

The critical developmental stages for individual human organs should be used to optimise data collection and interpretation.

Most reports and studies focus on lethal or serious major malformations using standard international medical terminology (most often WHO, ICD10). Minor malformations, especially more than one, may point to the risk also of major malformations and, therefore, information on minor malformations should not be dismissed. All information should be collated using MedDRA terminology, which has very extensive obstetrical and neonatal codes.

Universal pregnancy specific normal laboratory values should be used to enable judgements to be made quickly and accurately.

### 3.3.4 Potential “sources” of Information

Academia
Antenatal records
Drug companies
EuroMap Biomed group
EUROCAT Working Group
Maternal-fetal medicine networks
National Regulatory Authorities
Patient groups/mothers
Pharmacists
Professional societies, for example obstetricians, neonatologists, teratologists, geneticists, pathologists, dysmorphologists, other specialists, primary care, nurses/midwives
Teratology services:
Organisation of Teratogen Information Services (OTIS) and European network of Teratogen Information Services (ENTIS)
International Clearing House

### 3.3.5 Potential sources of data

Should RCTs be feasible in pregnant women, such studies should be performed and reported.

Cohort studies have the advantage that identification of patients can be done before the outcome is known. One type of cohort is collected in prospective pregnancy exposure registries, identifying both exposure to drugs in pregnant women and outcome data.

Possible sources for large European registry studies include the Swedish Medical Birth Registry, a national population based registry, accumulating data on drug exposure during pregnancy for the whole pregnant population of Sweden (>90,000 per annum).

Other types of registries could be organised to monitor a specific drug or to follow patients suffering from a specific medical condition. Such registries could be based on prescription data and pharmacy sales and could be set up by industry or academia or others.

Case control studies often have sufficient statistical power but they are subject to various types of recall bias, which are difficult to control for. The Hungarian case control surveillance of congenital abnormalities is a large case control data set that has been used for the analysis of more than 500 drugs.

The accuracy of the information will be highly dependent on the access to case records of mother and neonate, i.e. both exposure and outcome data must be available. The validity of all information is also dependent on the accuracy of diagnosis and recording.

Outcome data encompass both structural malformations and long-term effects. Some malformations are not always diagnosed immediately postpartum and, therefore, rates are significantly influenced by duration of follow-up.

Outcome data should also, if appropriate, be collected from autopsy results at stillbirth and on examinations of the fetus after spontaneous or induced abortion. The occurrence of a certain malformation may be influenced by the use of antenatal diagnosis and subsequent abortion, which is often the case with the most severe malformations.

All information should be collated using MedDRA terminology, which has very extensive obstetrical and neonatal codes.
4. SPECIFIC REQUIREMENTS AND RECOMMENDATIONS FOR REPORTING DATA AND ADVERSE OUTCOMES OF PREGNANCY EXPOSURE

4.1 Scope

As for all ADR (Adverse Drug Reaction) reporting, the MAH is responsible for reporting data on and adverse outcomes after pregnancy exposure with all medicinal products whatever the procedure of approval (i.e. centralized, national and mutual recognition procedures).

This section includes cases reported spontaneously by health-care professionals, cases originating from post-authorisation studies and those originating from the worldwide literature should be included.

4.2 Content of a report

The content of the report should be similar in adverse outcome reports (e.g. congenital malformation, neonatal disorder etc) and data on pregnancy exposure with or without ADR. For data of pregnancy exposure, the “pregnancy exposure” can be considered as the suspected adverse drug reaction.

It is essential for the MAH to provide as many data elements as possible for all cases to facilitate the evaluation. Specific data are necessary for the evaluation of the adverse event(s) such as the exposure to other teratogens (e.g. infections, maternal disease, environmental factors, drugs co-administered etc).

The minimum required data elements for the reports of adverse outcomes (e.g. congenital abnormality etc) and data on pregnancy exposure with or without ADR are similar to those required for any ADR report, i.e. an identifiable patient, an identifiable reporter, a suspected ADR and a suspected product. Information on drug exposure in pregnancy should include exact dates of exposure as accurately as possible as gestational length, specified by method of assessment and expressed as weeks + days, preferably calculated from early fetal ultrasound. This information is necessary to establish the causal relationship between the possible adverse events reported and the exposure to a product. For example, in the case of neural tube defect, a causal relationship with the suspected medicinal product can be considered unlikely if the treatment was used after 6+0 weeks of gestation because the closure of the caudal neural tube occurs on day 32 of gestation.

It is essential for the MAH to provide as many data elements as possible for all cases to facilitate the evaluation. Specific data are necessary for the evaluation of the adverse event(s) such as the exposure to other teratogens (e.g. infections, maternal disease, environmental factors, drugs co-administered etc).

In order to obtain standardized and detailed information from the reporter, the MAH is recommended to set up and use a structured questionnaire. A list of data elements to consider when establishing a questionnaire is provided in the annex 1 attached.

4.2.1 Particular situations:

- For cases of congenital malformation, special effort should be made by the MAH to get this medically confirmed and to collect and provide a full description of the congenital malformation, and whenever possible all investigations done in the paediatric ward and the medical records.
• For cases of spontaneous abortion, the time of occurrence and history of spontaneous abortion should be specified.

• For cases of termination of pregnancy after the 1st trimester of pregnancy, special efforts should be made by the MAH to obtain and provide the results of fetal autopsy and prenatal tests (e.g. ultrasound, amniocentesis, serum markers).

• For cases of late fetal death special efforts should be made to collect results of prenatal tests (e.g. ultrasound, amniocentesis, serum markers), results of the autopsy if available and other factors that may have had an impact on fetal loss (e.g. concomitant disease etc).

• For cases of paternal exposure, efforts should be made by the MAH to collect information on the father (i.e. date of exposure, occupation, environmental factors, medical history and drugs co-administered…) and on the mother (e.g. concomitant diseases, possible date of conception, course of pregnancy, treatments).

• Where medicinal products are known (or suspected) to induce teratogenic or fetotoxic effects during pregnancy and therefore contra-indicated (or not recommended) in pregnant women, the circumstances relating to the pregnancy should be documented (e.g. patient “not aware” of the risk, contraception failure etc).

The MAH is expected to provide follow-up of all cases:

**Exposure data**

Cases from health-care professionals should be monitored until the pregnancy outcome, e.g. live birth, fetal death, termination of pregnancy etc. Attempts should be made by the MAH to follow up cases from consumers through health care providers. In order to obtain follow-up information, the MAH is recommended to set up and use a specified procedure. This can consist of a telephone interview or mailing a questionnaire to the obstetrician/physician involved with the care of the patient after the expected date of delivery.

At the time of their first contact with the MAH, doctors should systematically be made aware of the usefulness of providing data on the outcome of pregnancy. The name and address of the obstetrician or another physician likely to have information on the outcome of the pregnancy should always be collected at this first contact.

**Adverse outcome of pregnancy exposure:**

The follow-up information of serious cases should be provided in the follow-up forms and transmitted to the Regulatory Authorities on an expedited basis.

The scope of a report of exposure in pregnancy does not end at birth. Efforts should be made by the MAH to obtain further information:

• In the case of congenital malformation, the MAH should try to provide an assessment of the severity of the malformation (surgery planned) and the final diagnosis, if available, e.g. the conclusions of a genetic counseling etc).

• In the case of fetotoxic effects (NSAID, angiotensin II receptor antagonists, neuroleptics etc), efforts should be made by the MAH to provide information on the outcome of the adverse events reported.
4.3 Reporting Forms

There is no special reporting form for data on adverse outcomes of pregnancy exposure. The MAH should use the same reporting form or method as used for ADR reporting in general, i.e. a reporting form acceptable to the competent authorities of the member states, or E2B format.

For medicinal products registered under the centralized procedure there is no special Individual Case Safety Report (ICSR) for cases of pregnancy exposure. However the ICSR (E2B format) includes a specific section for parent-child/fetus reports which contains information on parents (identification, age, last menstrual period - LMP- etc) and their relevant past medical and drug history.

In all cases MedDRA must be used for the medical terms.

All the specific data elements necessary for the assessment of cases of pregnancy exposure should be included in the narrative such as:

- The type of report: retrospective or prospective
  Prospective data of pregnancy exposure are data acquired prior to the knowledge of the pregnancy outcome or prior to the detection of a congenital malformation at prenatal examination (e.g. fetal ultrasound, serum markers etc).
  Retrospective data of pregnancy exposure are data acquired after the outcome of the pregnancy is known or after the detection of a congenital malformation on prenatal test.

- The exact timing of exposure during pregnancy (exact dates of exposure expressed as weeks + days, preferably calculated from early fetal ultrasound)

- Other risk factors: concomitant disease, co-medication, familial history of congenital anomaly etc..

- The results of examinations performed: fetal ultrasound, amniocentesis, laboratory tests etc..

4.4 Expedited reporting requirements

As for ADR reporting in general, expedited reports should be reported immediately and in no case later than 15 calendar days from receipt (see Vol. 9 of the Rules Governing Medicinal Products in the European Union).

This includes

- Reports of congenital anomaly(ies) in fetus, child
- Reports of fetal death
- Reports of spontaneous abortion
- Reports of ADRs in a newborn/neonate that is fatal, life-threatening, resulting in persistent or significant disability/incapacity or resulting in or prolonging hospitalization.

Other cases, i.e. reports of termination of pregnancy without information on congenital malformation and reports of pregnancy exposure without outcome data should not normally be reported on an expedited basis. These and reports of normal outcomes of pregnancy should be reported in the PSUR.
In certain special circumstances, the MAH can be requested to treat any reports of pregnancy exposure as expedited cases, e.g. pregnancy exposure to products contra-indicated in pregnancy because of a high teratogenicity potential (e.g. thalidomide, isotretinoin).

5. SPECIFIC REQUIREMENTS FOR THE PRESENTATION AND EVALUATION OF POST-AUTHORISATION DATA ON PREGNANCIES IN THE PSURS

5.1 Requirements
As stated in both the ICH E2C guideline as well as in the Notice to Marketing Authorisation Holders, part of Volume 9 of the Rules Governing Medicinal Products in the European Union, positive or negative experiences during pregnancy should be reported. These data will be reported in a section of chapter 9 of the PSUR. In addition, bibliographical data, cumulative figures together with a summary table should also be provided.

5.2 Post-Authorisation Data
Sources of pregnancy outcome data reported during post-authorisation (see section 3.3 Post-Authorisation Human Pregnancy Data) can be case reports, epidemiology studies, data from pregnancy registries etc.

Pregnancy outcomes are:
• Live birth, normal,
• Live birth, abnormal:
  Preterm birth
  Small for gestational age infants/ Intrauterine growth retardation
  Drug withdrawal syndrome in the neonate
  Malformations
  Morbidity
• Fetal death:
  Ectopic
  Miscarriage
  Stillbirth
• Termination of pregnancy

In cases of induced or spontaneous abortions and intra-uterine death, it should be mentioned whether the embryo/fetus had apparent congenital malformation.

5.2.1 Case reports
Case reports should be analysed separately from studies and registries. Case reports are mostly retrospective data, with an outcome of congenital malformation considered to be drug related.

Case reports can be spontaneous reports by health care professionals, published case reports, or case reports from studies and reports received from regulatory authorities. Cases from consumers are to be validated by a health professional. If not, these cases must be analysed and
presented separately from the others. Recommendations for the content of a case report have been provided before in the section 4.3.

The MAH should present the outcome of these case reports in a summary table and categorise the malformations according to the MedDRA SOC (Medical Dictionary for Regulatory Activities, System Organ Class. From 1 January 2003 the MAHs must report Adverse Events in MedDRA terms). The prevalence of the cases should be defined and analysed taking into account the background prevalence of pregnancy outcome in the general childbearing population.

Data collected prospectively should be separated from data collected retrospectively. Different ways for calculating the prevalence are given in the glossary.

In PSURs of drugs which have teratogenic/mutagenic potential or for new chemical entities, the MAH should, as well as the individual case reports received during the reporting period of a PSUR, analyse cumulative pregnancy data since authorisation.

5.2.2 Epidemiology studies

Epidemiological studies and their results should be discussed in detail in chapter 7 "Studies" of the PSUR with reference to the specific section in chapter 9, and summarised in chapter 9.

Epidemiological studies can be prospective or retrospective and, depending on the study outline, these data may be compared with registry data.

Results of epidemiological studies should be analysed as defined in the study protocol. Pregnancy outcome of congenital malformation, possibly suggestive of a treatment related effect, should be investigated for a possible trend and outcomes must be summarised.

5.2.3 Pregnancy Exposure

Data in registries should be analysed on a regular basis and the analyses should be discussed in the PSUR. Preferably, in case of registry for a certain product, the data lock point for the analysis will be the same as the data lock point of the PSUR. The data in those registries are in the majority of cases prospective; therefore the outcome results will contain also pregnancies with healthy infants born at term. Usually an analysis of the data collected by the Pregnancy Exposure Registry is performed periodically. In addition to the summary, the MAH should provide in the PSUR a copy of the last interim report of the Pregnancy Registry.

Pregnancy outcome should be summarised in a table.

5.2.4 Signal detection

The purpose of collection of pregnancy data is to detect certain trends in pregnancy outcome, which could be a signal for specific adverse effects. Therefore, such data should be analysed on a regular basis.

In the event of signal, the MAH is encouraged to provide Statement Report from an expert in teratology to accompany the PSUR.
ANNEX 1

DATA ELEMENTS TO CONSIDER WHEN ESTABLISHING A QUESTIONNAIRE OF REPORT OF EXPOSURE IN PREGNANCY

A. GENERAL INFORMATION
Prospective / Retrospective case
Date of initial contact with MAH
Source of information (e.g. pregnant woman, primary care physician, obstetrician, paediatrician, other)
Identification of reporter
Additional identification of the gynaecologist-obstetrician (if reporter is the patient or the primary physician), and the address of the place where the mother plans to be delivered

B. MATERNAL INFORMATION
Identification of patient
Date of birth (or age)
Occupation, education level
Weight, height

Obstetrical history:
Number of previous pregnancies and outcome (live birth, miscarriage, elective termination with specification of gestational length and context, late fetal death, ectopic pregnancy, molar pregnancy)
Previous maternal pregnancy complications
Previous fetal/neonatal abnormalities and type
History of subfertility

Maternal medical history
Risk factors for adverse pregnancy outcomes including environmental or occupational exposures.
e.g. hypertension, diabetes, seizure disorder, thyroid disorder, asthma, allergic disease, heart disease, depression or other psychiatric disorders, sexual transmitted disorders, hepatitis, AIDS (specify viral load, CD4 count), other.

Current pregnancy
Date of last menstrual period (LMP)
Gestational age at the time of the first contact with MAH (specify if based on ultrasound or LMP)
Gestational age at the time of drug exposure, preferably given as gestational week+days, based on ultrasound

Estimated date of delivery

Number of fetuses

Treatment for infertility (specify)

Medical product exposures (prescription drugs, OTC products, pregnancy supplements such as folic acid, multivitamins):
  - Name
  - Dosage & route
  - Date of first use, date of end of treatment, duration
  - Indication

Recreational drug use e.g. tobacco, alcohol, illicit drugs (specify amount and if stopped during pregnancy)

Results of serology tests, e.g. rubella, toxoplasmosis etc.

Complications during pregnancy and date (including any adverse drug reactions)

Disease course(s) during pregnancy and any complications

Antenatal check-up (specify dates and results), e.g. fetal ultrasound, serum markers (AFP, other), chorionic villi biopsy (CVS), amniocentesis

Delivery

Mode of delivery

Labour / Delivery complications (fetal distress, amniotic fluid abnormal)

Abnormal placenta

Family history

History of congenital abnormality, psychomotor retardation in the family (specify paternal/maternal and relationship)

Consanguinity between parents (specify degree)

C. PATERNAL INFORMATION if appropriate

General information

Age or birth date

Occupation

Medical history (if appropriate)

Medical products exposure
D. NEONATAL INFORMATION

Initial
Source of information
Date of receipt of information
Outcome of pregnancy and date (live birth, miscarriage, late fetal death, termination, ectopic pregnancy)
Date of birth
Gestational age at birth
Gender of neonate
Results of neonatal physical examination including:
   Weight at birth
   Length, head circumference at birth
Malformation/anomalies diagnosed at birth
Conditions at birth (including Apgar scores at 1 and 5 minutes, need for resuscitation, admission to intensive care unit)
Dysmaturity
Neonatal illness, hospitalisation, drug therapies

Follow-up
Source and date of information
Malformation/anomalies diagnosed since initial report
Developmental assessment
Infant illnesses, hospitalisations, drug therapies, breastfeeding

E. FETAL INFORMATION in case of elective termination, spontaneous abortion and late fetal death

Source of information
Date of receipt of information
Reason for termination
Gestational age at termination
Results of physical examination (gender, external anomalies) and pathology
ANNEX 2 – GLOSSARY

A) Terms used to define the fetus at the different stages of the pregnancy

- **Zygote**: the single diploid cell formed from the fusion of the ovum and spermatozoon.
- **Preembryo**: the first stage of prenatal (see below under fetus) development from conception until the end of implantation in the uterus and the start of organogenesis, i.e. until the postconceptional day 15 or gestational day 29.
- **Embryo**: the second stage of prenatal development including the organ-forming period (i.e. organogenesis) between gestational day 29 (beginning at 4 completed weeks) and gestational day 84 (i.e. the ending at 12 completed weeks of gestation). The critical period for most major congenital abnormalities includes the most vulnerable period of fetal development, i.e. organogenesis, which occurs visibly during weeks 4 to 12 of gestation. However, each congenital abnormality has its specific critical period, e.g. neural tube defect between the gestational days 29 and 42 (i.e. between days 15 and 28 post-conception).
- **Fetus**: this term has two meanings, the narrow definition of fetus reflects the stage of fetal development after organ-forming periods (i.e. organogenesis) until the birth while the broad definition of fetus covers the whole prenatal development from the conception until the birth.

B) Pregnancy outcomes

- **Pregnancy outcome**: the end products of pregnancy which include three main categories: fetal death, termination of pregnancy and live birth.
- **Fetal death** (intrauterine death, in utero death): death prior to complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of pregnancy; the death is indicated by the fact that after such separation the fetus does not show any evidence of life” (WHO, ICD). Fetal death includes different groups: early fetal death before 22 completed weeks of gestation, (ectopic pregnancy and miscarriage - spontaneous abortion or missed abortion), and late fetal death after 22 completed weeks of gestation = stillbirth.
- **Ectopic pregnancy** (extrauterine pregnancy – gravidity): early fetal death most often in the Fallopian tube.
- **Miscarriage** (spontaneous abortion, early fetal death): fetal death before 22 completed weeks of gestation.
- **Stillbirth** (late fetal death): fetal death after 22 completed weeks of gestation.
- **Termination of pregnancy** (induced abortion, elective abortion): artificial interruption of pregnancy.
- **Livebirth**: the complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of the pregnancy which, after such separation, breathes or shows any evidence of life. (WHO, ICD).
• Gestational age or length: the duration of gestation is measured from the first day of the last normal menstrual period. Gestational age is expressed in completed days or completed weeks (e.g. events occurring 280 to 286 days after the onset of the last menstrual period are considered to have occurred at 40 weeks of gestation).

• Last menstrual period (abbreviation LMP): according to international consensus, the gestational age is measured from the first day of the LMP.

• Birth weight: the initial weight of the infant at birth.

• Preterm birth (previous term: premature birth): less than 37 completed weeks (less than 259 days) of gestation.

• Term birth: from 37 to less than 42 completed weeks (259 to 293 days).

• Post-term birth: 42 completed weeks or more (294 days or more).

• Low birth weight: less than 2,500 gram (up to and including 2,499 g) of body weight of the newborn at birth.

• Intrauterine growth retardation (small for gestational age): the observed weight of a live born infant or size of a fetus is lower than expected on the basis of gestational age.

C) Congenital malformations (birth defects)

• Congenital anomaly (synonym in the US: birth defect): morphological, functional and/or biochemical developmental disturbance in the embryo or fetus whether detected at birth or not. The term congenital anomaly is broad and includes congenital abnormalities, fetopathies, genetic diseases with early onset, mental retardation, etc.

• Congenital abnormality (structural birth defect, sometimes congenital malformation, fetal defect): a consequence of error of morphogenesis, i.e. structural-morphological defect, grossly or microscopically present at birth whether detected at birth or not.

• Congenital malformation: a morphological defect of an organ, part of an organ, or larger region of the body resulting from an intrinsically abnormal developmental process.

• Isolated congenital abnormality: a single localised error of morphogenesis.

• Multiple congenital abnormalities: a concurrence of two or more different morphogenetical errors, i.e. component congenital abnormalities in the same person.

• Teratogens: environmental factors which can cause congenital abnormalities.

• Major malformation: a lifethreatening structural anomaly or one likely to cause significant impairment of health or functional capacity and which needs medical or surgical treatment. The incidence of major malformation recognized at birth among liveborn infants is 2%-4% in most series published.

• Minor malformation: relatively frequent structural anomaly not likely to cause any medical or cosmetic problems.

• Prevalence is the number of instances of an occurrence in a given population at a designated time. For convenience these rates are usually multiplied by 1000 or 10,000 to avoid small decimal numbers. The numerator is the number of cases of the subject of interest. The denominator is the population from which the numerator came.
Live birth prevalence rate:
Number of cases among live born infants x 1000
Total number of live born infants

Birth prevalence rate:
Number of cases among live and stillborn infants x 1000
Total number of (live + still) born infants

Total prevalence rate:
Number of cases among live births, stillborn and terminated pregnancies x 1000
Number of live births, stillbirths and terminated pregnancies