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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON

THE EXPOSURE TO MEDICINAL PRODUCTS DURING PREGNANCY:

NEED FOR POST-AUTHORISATION DATA

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1. INTRODUCTION

The clinical trial program of a medicinal product under development rarely includes pregnant women, (unless the product is intended specifically for use during pregnancy), however, some pharmacological treatments cannot be discontinued during pregnancy. In most clinical trials in which women of childbearing age are included, effective contraception must be used. For this reason, the only data available to evaluate reproductive risk when a new medicinal product is approved for marketing is virtually from non-clinical studies, and although these non-clinical studies can be useful to predict human risk, the extent of prediction needs to be taken with caution.

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

Once a product is marketed, 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 foetus. Conversely, data on pregnancy exposure can also establish that the foetal toxicity of a product is limited.

Use of medicines in pregnancy is not uncommon and different studies have shown that there is a high variability in the frequency of drug use during pregnancy among different countries. It is also 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.

1.1 Scope of the guideline

This guideline aims at providing criteria to select medicinal products for which active surveillance for collecting post-authorisation data in pregnancy is necessary. It provides 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 guideline also includes detailed recommendations regarding presentation of data collected on exposure in pregnant women.

The guideline relates in particular to new products, for which 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 Marketing Authorisation Holder (MAH) at the time of the MA application. The aim of these specifications is that the MAH proposes 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.

It is recommended that a similar pharmacovigilance plan is developed for established products, when a new major safety concern has arisen, and for “old products”, for which reliable data in animals are lacking and experience in humans is poorly documented.

The guideline also concerns the use of medicinal products in men, as products might have effects on the foetus via semen due to their mutagenic or teratogenic potential.

1.2 Aspects not covered in the guideline

It should be noted that this guideline will not cover specific aspects of safety and efficacy of medicinal products authorised for pregnancy-related symptoms and disorders or pro-fertility drugs. Other products like herbal medicines and the use of medicinal products during breast-feeding are not covered either in this guideline.

1.3 Legal basis

This guideline should be read in conjunction with the Council Regulation (EEC) 2309/93 (Title II, Chapter 3), European Parliament and Council Directive 2001/83/EC, as amended (Title IX),

Commission Regulation (EC) 540/95, Council Regulation (EEC) No 2309/93 and 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)
- ICH topic E2B(M): Note for Guidance on Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports (CPMP/ICH/287/95,– adopted in November 2000)
- ICH topic E2B(M): Questions and answers to CPMP/ICH/287/95. (CPMP/ICH/3943/03, adopted in November 2003)
- ICH topic E2A: Note for Guidance on Clinical Safety Data Management: Definitions and Standards for expedited reporting (CPMP/ICH/377/95, 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)
- All applicable ICH guidelines and standards for electronic reporting of Individual Case Safety Reports (i.e. M1, M2).
- The 'Note for Guidance on the Electronic Data Interchange (EDI) of Individual Case Safety Reports (ICSRs) and Medicinal Product Reports (MPRs) in pharmacovigilance during the pre- and post- authorisation phase in the European Economic Area (EEA)', Doc. Ref. EMEA/115735/2004 (adopted at Community level in September 2004).
- The EMEA guidance 'Technical Documentation - EudraVigilance Human Version 7.0 Processing of Safety Messages and ICSRs' (Doc. Ref. EMEA/H/20665/04) (adopted at Community level in July 2004).
- 'Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions (EudraVigilance - Clinical Trial Module), (Doc. Ref. ENTR/CT4, Revision 1, adopted at Community level in April 2004).
- Guideline on Risk Management Systems for Medicinal Products for human use (EMEA/CHMP/96268/2005).

2. GENERAL CONSIDERATIONS REGARDING THE NEED TO COLLECT INFORMATION

2.1 Background

The majority of medicinal products or chemical substances administered to a pregnant woman could have effects on the foetus either before the placenta is fully developed or subsequently, if they can cross the placenta to at least some extent. Substances used for therapeutic purposes in the mother have the potential to reach the foetus with the consequential potential for harmful effects, depending on whether the rate and extent of drug transfer results in sufficient concentrations within the foetus.

Medicinal products may 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 teratogenic agent during the period of organogenesis may induce major malformation, growth retardation or death, while exposure during the second or third trimester may induce growth retardation, renal insufficiency, neurological disorders, stillbirth, etc. On the other hand, exposure to a teratogenic agent during the first two weeks of pregnancy (3rd and 4th gestational week) may lead either to the death or to a normal preembryo according to the "all or nothing rule"; at this period zygotes and blastocysts contain omnipotent stem cells without any differentiation, therefore, teratogenic agents may lead to seriously damaged preembryos, which will not survive, or to less seriously damaged preembryos, which will survive with complete regeneration.

Drug treatment of male patients 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.

Two important conclusions can be drawn from the above considerations:

In order to minimise the foetal 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 requires treatment, or a condition that untreated may pose significant risk to the foetus.

In order to optimise the knowledge about any potential teratogenic or embryotoxic/foetotoxic effects of a medicinal product and the doses and concentrations at which such effects will develop, it is desirable to gather information about all medicinal products taken by pregnant women.

2.2 Assessing the need for information on drug exposure

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

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

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

  There is a special need for information in situations when available treatment options are already limited due to known or suspected risks established from animal studies or human experience. Examples of these situations include: antiepileptic, antineoplastic, antithyroid agents, antiretrovirals. This 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, although not necessarily required, is frequently given, with or without prescription. This group mainly comprises treatment of common symptoms such as constipation, fatigue, mild to moderate forms of allergic symptoms, common cold, fever, 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/embryo-foetotoxic signals. On the other hand, medicinal products for which well-conducted epidemiological studies in pregnant women failed to demonstrate a risk to the foetus may be exempted.

- Treatment with drugs belonging to a class of substances having a similar chemical structure or mechanism of action to:

- Substances of which the teratogenic, embryotoxic, foetotoxic or mutagenic effects in humans is suspected from case reports and animal studies;

- Substances of which the potential for teratogenic or embryotoxic/foetotoxic or mutagenic effects in humans has already been established;

  In these cases, it is of special importance to monitor any exposure to the substance in case pregnancy is diagnosed or appropriate contraceptive measures were either not taken or failed.

- Drugs either representing a completely new chemical entity or exhibiting a new mode of action (e.g. biotechnology products), if not already covered by the previous categories.

2.3 Specific recommendations for surveillance

The medicinal products for which there is a special need for surveillance during pregnancy are identified according to the above-mentioned criteria. For these medications, the MAH should develop appropriate measures of active surveillance as laid down in a risk minimisation plan. The choice of method of surveillance will depend on how frequently the medicinal product is used, the type of adverse outcome to be monitored (e.g. birth defects, malignancy, psychomotor retardation) and the magnitude of the risk.

A commitment from the MAH to introduce such pro-active monitoring is expected especially for those products referred to under the first and third bullet points above.

In general, exposure during the whole pregnancy should be monitored. For medicinal products with long 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.

In accordance with ICH E2E on Pharmacovigilance Plans and the CHMP Risk Management System Guideline, the MAH should describe in the safety specifications a summary of the identified risks of a drug, potential risks, and missing information for pregnancy. The MAH should take into account information such as possible teratogenicity or foetotoxicity observed in preclinical studies, or class effects (like neonatal reactions observed in a given drug class, e.g. withdrawal syndrome)
In all cases, the MAH should state which specific actions will be taken for risk management and on what basis these actions will be reported upon.

3. REVIEW OF POTENTIAL SOURCES OF HUMAN PREGNANCY DATA

This section provides a list of the key methods which can be used to evaluate the potential risk of exposure to a specific medicinal product during pregnancy (or to provide missing information). The list is not all-inclusive.

3.1 Human Pregnancy Data from Pre-Authorisation studies

In clinical trials which include female patients of reproductive age, there may be occasional inadvertent pregnancy exposure to the medicinal product. This inadvertent exposure is usually restricted to the early first trimester. Efforts should be made to collect data on the drug effects as well as the outcome for both mother and foetus.

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, opportunities for collecting pharmacokinetic information, 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 Human Pregnancy Data collected Post-Authorisation

3.2.1 Sources of data information

3.2.1.1 Spontaneous reports / Case series

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

Sources include databases of 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. 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 guideline.

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

3.2.1.2 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 the 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 progress 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 statistical power by linking the Swedish Medical Birth Registry to a cancer registry.

3.2.1.3 Registries

3.2.1.3.1 Birth defect registries

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

3.2.1.3.2 Pregnancy registries

Prospective pregnancy registries for screening and analysis have been used to identify and estimate risks associated with exposure to medicinal products. 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).

Registries may focus on different aspects, depending on whether they are set up and coordinated centrally by government agencies, such as the Swedish Medical Birth Registry, by industry or academia. Thus, a registry can be organised to monitor a specific medicinal product, 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.

Those set up by industry to monitor specific medicinal products such as the AntiRetroviral Pregnancy Registry are named "pregnancy registry" but do not correspond to a "registry" from a pharmaco-epidemiological viewpoint since they don't register all cases of pregnancy exposure to the concerned medicinal product. Indeed they are based on voluntary reporting.

3.2.2 Clinical studies

3.2.2.1 Randomised controlled trials (RCTs)

Where the study is in the best interest of both mother and infant, an RCT may be feasible. Despite barriers, particularly the ethical considerations, conducting RCTs in pregnant women, there are occasional reports of such studies in the literature (e.g. asthma, HIV). Studies may also aim to prove a beneficial effect of a medicinal product on the foetus (e.g. 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).

3.2.2.2 Comparative observational studies

3.2.2.2.1 Cohort studies

There are several publications from cohort studies investigating the effects of drugs in pregnant women. The advantage with cohort studies is that identification of patients before the outcome is known will eliminate recall bias. Cohort studies need to be adequately controlled for underlying medical conditions, disease severity, multiple medications and demographic factors. Despite the fact that these conditions may be difficult to fulfil, cohort studies may be interpretable and useful.

3.2.2.2.2 Case control studies

These studies identify individuals with a specific outcome (e.g. a congenital malformation), against a control group and assess both groups with regards to exposure. In the case of specific malformations, these studies often have sufficient statistical power, but they might be subject to recall bias if data are collected retrospectively.

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). It is the largest case control data set in the world and has been used for the analysis of more than 500 drugs.

3.2.2.3 Study areas of specific interest

3.2.2.3.1 Foetal therapy studies

Efficacy and safety information from studies with predefined outcomes (e.g. use of corticosteroids in mothers with preterm labour to induce foetal pulmonary maturation), should be collected. Outcome measures include foetal loss and infant mortality rates, gestational age at delivery (as determined by LMP and/or ultrasound), birth weight, premature rupture of membranes, neonatal complications, congenital malformations and developmental delay.

3.2.2.3.2 Pharmacokinetic studies

A number of studies in the 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 for which a benefit from therapy is known, particularly addressing the late second and third trimesters and early post-partum period. Population PK studies have been suggested as a preliminary step prior to conducting more invasive and intensive PK studies (or possibly as their replacement).

3.2.2.3.3 Pharmacogenetic studies

It has been suggested 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.

3.2.3 Other Potential sources of information

Some sources providing information on congenital birth defects are listed below:

- Organisation of Teratogen Information Services (OTIS) (http://www.teratology.org)
- European network of Teratogen Information Services (ENTIS) (http://www.entis-org.com)
- EUROCAT (http://www.eurocat.ulster.ac.uk)
- International Clearinghouse for Birth Defects Monitoring Systems (http://www.icbd.org)
- European collaboration of craniofacial anomalies (http://www.eurocran.org)

Apart from these sources, information may be available elsewhere, for example through regulatory authorities, pharmaceutical companies, national antenatal records, patient societies, professional societies, (e.g. obstetricians, neonatologists, teratologists, geneticists, pathologists, pharmacists, primary care, nurses/midwives).

3.3 Quality of collected data

3.3.1 Exposure data

All 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. High levels of recruitment have been achieved using direct prospective enrolment, either specifically for pregnancy exposure studies, or in addition to routine contact with a healthcare provider such as at prenatal care visits.

Ideally, medicinal products 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 foetal development.

3.3.2 Outcome data

Adverse outcome data of foetal exposure comprise both structural malformations, ('typical' birth defects, often – but not always – detected in the neonatal period) and non-structural or long-term functional effects (not easily detected in the immediate neonatal period) that can be potentially important but also difficult to detect or define.

Some cardiac, renal and intestinal malformations are not always diagnosed immediately postpartum, and incidence is significantly influenced by duration of follow-up and availability of diagnostic tests. Therefore, long-term follow-up is recommended when possible and appropriate.

It is important to note that the incidence of a given 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 abnormalities incompatible with life, it is important to collect information on autopsy results at stillbirth and, if possible, on examinations of the foetus after spontaneous or induced abortion.

Additionally, reviewing birth certificates is not an accurate method of ascertaining pregnancy outcome as individuals who have not examined the neonate often complete the forms, while neonatal hospital records are more reliable. However, diagnoses may arise or can be modified as the child is more thoroughly examined and undergoes additional testing. Involvement of mothers could minimise lack of 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 to provide not only reassurance but also information on possible exposure times when other outcomes have been abnormal.

3.3.3 Data standardisation

The validity of information is dependent on the accuracy of diagnosis and recording. Exposure dates are important, 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 if several occur in a neonate, may point to the risk of major malformations and, therefore, information on minor malformations should not be dismissed..

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

4. REPORTING DATA AND ADVERSE OUTCOMES OF PREGNANCY EXPOSURE

4.1 Scope

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

Cases reported spontaneously by health-care professionals, cases originating from pre- or post-authorisation studies and those originating from the worldwide literature should be included.

4.2 Content of a report

4.2.1 General recommendations

It is essential that MAHs collects and provide as many elements as possible for all cases to facilitate the evaluation.

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 medicinal product.

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. foetal ultrasound, serum markers).

  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.

- Information on exposure to medicinal products during pregnancy should include dates of exposure as accurately as possible. Gestational length, should be specified by method of assessment and expressed as weeks + days, preferably calculated from early foetal ultrasound. This information is necessary to establish the causal relationship between the adverse events reported and the period of exposure to a product.

- Exposure to other teratogens (e.g. infections, maternal disease, environmental factors, co-administered medicinal product), familial history of congenital anomaly etc.

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

In order to obtain standardised and detailed information from the reporter, MAHs are recommended to set up and use a structured questionnaire. A list of data elements to be considered when establishing a questionnaire is provided in annex 1.

In certain circumstances, MAHs can be requested to submit the structured questionnaire to regulatory agencies (e.g. for products with a highly teratogenic potential).

4.2.2 Special situations:

Special efforts should be made by the MAH in the following situations:

- For cases of congenital malformations, to get this medically confirmed and to provide a full description of the congenital malformation. Whenever possible all investigations done in the paediatric ward and the medical records should be provided.

- For cases of spontaneous abortion, to specify the time of occurrence and history of spontaneous abortion.

- For cases of termination of pregnancy after the first trimester of pregnancy, to obtain and provide the results of foetal autopsy and prenatal tests (e.g. ultrasound, amniocentesis, serum markers).

- For cases of late foetal death, 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 foetal loss (e.g. concomitant disease).
- For cases of paternal exposure, to collect information on the father (e.g. 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 foetotoxic effects and are 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) and MAH should provide information on the outcome of the pregnancy.

4.2.3 Follow-up data

At the time of their first contact with the MAH, health care professionals should systematically be made aware of the usefulness of providing data on both the exposure and the outcome of pregnancy.

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

The scope of a report of exposure in pregnancy does not end at birth. In case of congenital anomalies, 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 counselling).

4.3 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 foetus, child
- Reports of late foetal 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 hospitalisation.

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 PSURs.

In certain circumstances, MAHs can be requested to treat any reports of pregnancy exposure as expedited cases, e.g. pregnancy exposure to products contra-indicated in pregnancy due to a high teratogenic potential (e.g. thalidomide, isotretinoin).

In accordance with Directive 2001/83/EC, as amended and Regulation (EC) No 726/2004, the MAH should use the same method to submit this data as used for ADR reporting, therefore save in exceptional circumstances, these reports should be transmitted electronically using the ICH E2B(M) format through the EudraVigilance system.

The ICH E2B(M) format includes a specific section for parent-child/foetus reports that contains information on the parent and this section should be completed in accordance with the ICH E2B(M) specifications. The route of administration of the drug for the child would normally be transplacental, in cases where the father has taken the drug the route of administration should be marked as unknown. The route of administration of how the parent took the drug should be captured in the field ICH E2B(M) "parent's route of administration". Specific recommendations for the transmission of Individual Case Safety Reports (ICSR) of pregnancy exposure are provided in annex 2. Since the E2B(M) fields do not capture all the elements listed in Annex 2, In all cases a case narrative capturing these data elements should systematically provided with the case report.

Specific recommendations for the transmission of Individual Case Safety Reports (ICSR) of pregnancy exposure are provided in annex 2.

In all cases, the MedDRA terminology which has very extensive obstetrical and neonatal terms must be used for the medical terms.

The follow-up information of serious cases should be transmitted to regulatory authorities on an expedited basis.

5. REPORTING PREGNANCY EXPOSURE IN PSURS

5.1 Requirements

As stated in both the ICH E2C guideline as well 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 (see annex 3) should also be provided.

In case there is an issue regarding for instance teratogenicity , foetotoxicity , neonatal adverse reactions stated in the Pharmacovigilance Plan and/or Risk Management Plan for a certain active substance the MAH will provide an update on these issues in every PSUR to be submitted.

5.2 Post-Authorisation Data

Sources of pregnancy outcome data reported during post-authorisation (see section 3.2 Post-Authorisation Human Pregnancy Data) can be case reports, epidemiology studies, data from pregnancy registries etc.

Pregnancy outcomes may be:

- Live birth, normal,
- Live birth, abnormal:

  Pre-term, term, post-term birth

  Small for gestational age infants/ Intrauterine growth retardation

  Drug withdrawal syndrome in the neonate

  Malformations

  Morbidity
- Foetal 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/foetus had apparent congenital malformation.

5.2.1 Case reports

Case reports should be analysed separately from studies and registries. Case reports can be spontaneous reports by healthcare professionals, published case reports, or case reports from studies and reports received from regulatory authorities. Cases from patients are to be validated by a healthcare 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 above in 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 (see annex 4).

In PSURs of products which have suspected teratogenic/mutagenic potential, or new chemical entities, the MAH should enclose the individual case reports received during the reporting period of a PSUR, and also analyse and provide cumulative pregnancy data.

5.2.2 Epidemiology studies

Epidemiological studies, as described in the pharmacovigilance specifications, 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.

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 in chapter 9.

5.2.3 Pregnancy registries

Data from registries (internal or external) should be analysed on a regular basis and the analyses should be discussed in 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. Preferably, in case of registry for a given product, the data lock point for the analysis will be the same as the data lock point of the PSUR.

In special situations (e.g. exposure to known or suspected teratogens/foetotoxic compounds) a report of the data analysed from the Registry may be requested in intervals more frequent than the PSURs.

Pregnancy outcome should be summarised in a table (see annex 3).

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 a signal is identified, the MAH is encouraged to inform the CHMP and/or the relevant National Competent Authorities. In addition, the MAH is encouraged to provide Statement Report with a scientific assessment of this signal from an appropriate expert with or shortly after submission of the PSUR.

ANNEX 1 - QUESTIONNAIRE TO COLLECT INFORMATION ON PREGNANCY EXPOSURE

This annex provides a number of possible parental and neonatal data elements from which relevant points can be selected when establishing a questionnaire of pregnancy exposure to medicinal products. What is to be collected should be defined appropriately according to the specific condition / disease or exposure of interest. It is acknowledged that, in some instances, data may be difficult to obtain, but, in general, the more comprehensive the data collection, the more reliable will be the results.

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 deliver

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 foetal death, ectopic pregnancy, molar pregnancy)
- Previous maternal pregnancy complications
- Previous foetal/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 foetuses
- Treatment for infertility (specify)
- Exposure to products subject to medical prescription, 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. foetal ultrasound, serum markers (AFP, other), chorionic villi biopsy (CVS), amniocentesis

Delivery

- Mode of delivery
- Labour / Delivery complications (foetal 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 foetal death, elective termination, ectopic pregnancy, molar 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. FOETAL INFORMATION in case of elective termination, spontaneous abortion and late foetal 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 - INDIVIDUAL CASE SAFETY REPORTS (ICSR) OF PREGNANCY EXPOSURE

For additional information, refer to the ICH guideline topic E2B(M)

1st situation:	**Adverse drug reaction (ADR) reported in mother**	
	Spontaneous abortion	1 case « mother »
	Foetal death without information on malformation	1 case « mother »
	Foetus with defects	2 cases: 1 case « mother » and 1 case « foetus » but cases linked (see section A.1. 12 in guideline ICH E2B)
	Birth defects or ADR in baby	2 cases: 1 case « mother » and 1 case « baby » but cases linked (see A 1 12 ICH E2B)
	No ADR in child	1 case « mother »

2nd situation:	**No ADR in mother**	
	Spontaneous abortion	1 case « mother »
	Foetal death without information on malformation	1 case « mother »
	Foetus with defects	1 case « foetus »
	Birth defects or ADR in baby	1 case « baby»
	No ADR in child	No case

Particular situation:	**twins**	1 case for each twin

ANNEX 3 - SUMMARY TABLE OF PREGNANCY OUTCOME

This table must be regarded as the most extended table regarding timing of exposure, data should be provided as available. However, for teratogenic products the table should be filled in completely.

Pregnancy outcome	Prospective cases Number					Retrospective cases Number				
	Timing of exposure in pregnancy					Timing of exposure in pregnancy				
	Before conception	1st trimester	After 1st trimester	During all pregnancy	Unknown	Before conception	1st trimester	After 1st trimester	During all pregnancy	Unknown
Ectopic pregnancy										
Spontaneous abortion										
Elective termination (foetal defects)										
Elective termination (no foetal defects or unknown)										
Stillbirth with foetal defects										
Stillbirth without foetal defects										
Live birth with congenital anomaly										
Live birth without congenital anomaly										
Total										

ANNEX 4 - DEFINITIONS

A) Terms used to define the foetus 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 foetus) 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 foetal 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).
- Foetus: this term has two meanings, the narrow definition of foetus reflects the stage of foetal development after organ-forming periods (i.e. organogenesis) until the birth while the broad definition of foetus covers the whole prenatal development from the conception until the birth.

B) Pregnancy outcome[1]

- Pregnancy outcome: the end products of pregnancy which include three main categories: foetal death, termination of pregnancy and live birth.
- Foetal 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 foetus does not show any evidence of life (WHO ICD 10). Early foetal death (before 22 completed weeks of gestation) comprises ectopic pregnancy and miscarriage and late foetal death (after 22 completed weeks of gestation) is known as stillbirth.
- Ectopic pregnancy: extrauterine pregnancy, early foetal death most often in the Fallopian tube.
- Miscarriage: spontaneous abortion, molar pregnancy.
- Termination of pregnancy (induced abortion, elective abortion): artificial interruption of pregnancy.
- Live birth: 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 10).
- 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.
- Pre-term birth (previous term: premature birth): less than 37 completed weeks (less than 259 days) of gestation.

[1] According to WHO-ICD 10, national regulations might be different

- 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 foetus is lower than expected on the basis of gestational age.

C) Congenital anomalies (birth defects)

- Congenital anomaly: morphological, functional and/or biochemical developmental disturbance in the embryo or foetus whether detected at birth or not. The term congenital anomaly is broad and includes congenital abnormalities, foetopathies, genetic diseases with early onset, developmental delay, etc.
- Congenital abnormality (structural birth defect, sometimes congenital malformation, foetal 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 abnormalities: a life threatening 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 abnormalities recognized at birth among liveborn infants is 2%-4% in most series published.
- Minor anomalies: relatively frequent structural anomaly not likely to cause any medical or cosmetic problems.
- Prevalence: 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:

$$\frac{\text{Number of cases among live born infants}}{\text{Total number of live born infants}} \times 1000$$

Birth prevalence rate:

$$\frac{\text{Number of cases among live and stillborn infants}}{\text{Total number of (live + still) born infants}} \times 1000$$

Total prevalence rate:

$$\frac{\text{Number of cases among live births, stillborn and terminated pregnancies}}{\text{Number of live births, stillbirths and terminated pregnancies}} \times 1000$$