Medicinal products during pregnancy and lactation – an issue of risk management

Wissenschaftliche Prüfungsarbeit
zur Erlangung des Titels
„Master of Drug Regulatory Affairs“
der Mathematischen-Naturwissenschaftlichen Fakultät
der Rheinischen Friedrich-Wilhelms-Universität Bonn

vorgelegt von
Dr. Anita Jörg
aus München

Bonn 2007

1. Referentin und Betreuerin:	Dr. Birka Lehmann
2. Referentin:	Prof. Dr. Barbara Sickmüller

Abbreviations

ADEC	Australian Drug Evaluation Committee
ADME	Drug Absorption, Distribution, Metabolism and Excretion
ADR	Adverse Drug Reaction
CNS	Central Nervous System
D	Dalton
DNA	Desoxyribonucleinacid
EU	European Union
EU-RMP	EU-Risk Management Plan
FASS	Swedish System of Approved Drugs
FDA	United States Federal and Drug Administration
HA	Health Authority(ies)
HIV-1	Human Immunodeficiency Virus Type 1
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICSR	Individual Case Safety Report
MAH	Marketing Authorisation Holder
NOAEL	No Observed Adverse Effect Level
NTA	Notice to Applicants
pH	Concentration of H^+-ions
pKa	- log K_a
PSUR	Periodic Safety Update Report
SmPC	Summary of Product Characteristics
US	United States of America
WHO	World Health Organization

Table of Contents

1 Introduction 5
1.1 Placental function during pregnancy 5
1.2 Breastfeeding 6
1.3 Congenital malformations 6
1.4 Human teratogenesis 7
1.5 Fundamentals of teratogenicity 7
2 Historical perspective 9
2.1 Thalidomide 9
2.2 Isotretinoin 11
2.3 Bendectin 11
3 Current process to classify safety and risk of medicinal products in pregnant women 12
3.1 Assessing the risk for humans by means of animal studies 13
3.1.1 Fertility and embryonic development 15
3.1.2 Embryofetal development 15
3.1.3 Prenatal and postnatal development including maternal function 15
3.1.4 Juvenile animal studies 15
3.2 Human Pregnancy Data from Pre-Authorisation studies (Clinical trials) 16
3.2.1 Regulatory requirements for including women of childbearing potential 16
3.3 Problems and difficulties to conduct clinical trials in pregnant women are multiple 17
3.3.1 Physiological changes during pregnancy 18
3.3.2 Ethical considerations 18
3.3.3 Practicalities and logistics 19
3.3.4 Clinical trials in pregnant women with severe chronic diseases 19
3.4 The need to collect post-authorisation data 20
3.5 Assessment of potential risk and conclusion 24
3.5.1 Assessment of non-clinical data 24
3.5.2 Assessment of clinical data 24
3.5.3 Assessment of a malformative effect 25
3.5.4 Administration during lactation 25
3.5.5 Conclusion of indicated risk 26
3.6 Labelling of medicinal product appropriate to the identified risk 27
3.6.1 Summary of Product Characteristics 27
3.6.2 Package Leaflet and labelling 28
3.7 Risk classification systems of different countries 29
3.8 Pharmacovigilance activities 32

3.8.1 Risk Management System 33
3.8.2 Safety Specifications 33
3.8.3 Pharmacovigilance Plan 34
3.8.4 Risk Minimisation Activities 34
3.8.5 Post-marketing surveillance 35
4 Conclusion 36
5 Summary 41
6 References 43
7 Annex – Definitions 50

1 Introduction

According to statistical inquests it is estimated that 15 to 50 percent of expectant mothers take pharmaceutical agents in the first trimester of pregnancy, often not being aware of their pregnancy. Considering the sensitive phase of organogenesis, particularly in the first three months of pregnancy the consequences may be fatal (Paulus 1999). Outweighing the potential risk expecting mothers and their physicians are mostly confronted with standard pharmaceutical labelling such as “safe use in pregnancy has not been established” and therefore “the medicinal product should only be used in pregnant women if the potential benefit justifies the possible hazards”. This may cause women to consider or even terminate the pregnancy.

The profound effects that drugs[1] and other chemicals can have on the fetus were brought into clear focus with the thalidomide disaster in the early 60s (Dally 1998). This sedative/hypnotic medicinal agent was administered to women during the first trimester to treat nausea and vomiting in early pregnancy. Many babies were born with severe deformities of arms and legs and other malformations. History proved thalidomide exposure to be the causative link to these birth defects (Dally 1998; Bernstein 1997; Lenz 1961). This tragedy brought attention to the possibility that other medicinal products could have similar effects on the fetus.

1.1 Placental function during pregnancy

The placenta forms a physical barrier between mother and child during pregnancy. The major function of the placenta is to transfer nutrients and oxygen from the mother to the fetus, and to assist in the removal of waste products from the fetus to the mother (Syme et al. 2004). In addition, it serves as an endocrine organ providing hormones, peptides and steroids, and it separates the circulation of two distinct individuals protecting the fetus from xenobiotics in the maternal blood (Syme et al. 2004).

It has been shown that any drug or chemical substance administered to the mother is able to cross the placenta to some extent, unless it is destroyed or altered during passage, or its molecular size and low solubility limit transplacental transfer. Drugs cross the placenta mainly via passive diffusion (Syme et al. 2004). Lipophilic, unbound and unionized drugs with a low molecular weight (<500-600 Dalton [D]) cross biological membranes more easily than lipophobic, polar compounds bound to plasma proteins (Audus 1999; Syme et al. 2004). Drugs with a molecular weight >1000 D cross the membrane very poorly. Since most drugs have a molecular weight <500 D, size rarely limits the rate of drug transfer through the placenta (Audus 1999; Syme et al. 2004). The drug may interfere with the passage of nutrition across the placenta leading to fetal malnutrition since the placenta expresses several transporter proteins, which are relevant in nutrient transfer to the fetus and may also actively contribute to the functional barrier between maternal and fetal circulations (Knipp et al. 1999; Ganapathy et al. 2000). While transporters, such as P-glycoprotein, may protect the embryo or the fetus from toxic exposures by actively preventing xenobiotics from entering the fetal compartment, inhibition of function of these proteins may increase fetal susceptibility to drug-induced teratogenicity, and some of them may actually facilitate drug transportation

[1] In the following text the US term ‘drug’ is maintained in citations of original literature. In the entirely text the EU term ‘medicinal product’ is used.

from the mother to the fetus (Audus 1999; Ganapathy et al. 2000; Ganapathy and Prasad 2005; Mölsä et al. 2005).

The molecular mechanism by which medicinal products exert teratogenic effects are poorly understood. Medicinal product may have a direct effect on embryonic development and result in specific abnormalities or may affect maternal receptors with indirect effects on the fetus.

1.2 Breastfeeding

It has been shown that many drugs taken by the nursing mother are passed to the child to a certain degree (Committee on Drugs 1994; Koren et al. 1998). The extent of drug excretion into the milk is dependent on several factors: pH of breast milk and plasma as well as chemical properties like pKa of the drug, solubility, degree of ionization and molecular weight of the drug (Loebstein et al. 1997; Joshua 1989). In general, pharmaceuticals that are weak bases accumulate in the breast milk, and most medicinal products taken by the mother in therapeutic doses can be found in the milk. Despite the fact that these low concentrations normally do not harm the newborn, it is a matter of concern if the drug requires renal or hepatic metabolism (Loebstein et al. 1997). Further, the developing neonates metabolize drugs differently, depending on age (Loebstein and Koren 1998). In literature the recommendations regarding medicinal products during lactation are often conflicting since it is not always known how much of a given medicinal product passes into breast milk.

1.3 Congenital malformations

According to statistical inquests about 2 to 3 % of newborns are diagnosed with severe anatomical malformations. Major congenital malformations are defined as physical defects causing a significant functional disturbance and requiring medical or surgical intervention (Kalter 2003). Within the first 5 years of life further 2 to 3 % of malformations are manifested resulting in an incidence of 4 to 6 %. The reasons are manifold. Table 1 provides a detailed overview.

Table 1. Congenital malformations in humans in percent*

Aetiology	**Percent**
Monogenetic diseases	8 to 20 %
Chromosomal anomaly	3 to 10 %
Anatomical factors including anomalies of the uterus and twin gravidity	up to 3 %
Chemical and physical reasons including medicinal products and drug abuse	up to 2 %
Maternal diseases including infections	up to 3 %
Polygenetic reasons, combination and interaction of exogenous and endogenous factors	up to 49 %
Unknown reasons, spontaneous developmental disturbances	33 to 70 %

*Due to differing study results the accounts vary strongly, however, it gives a rough impression of the proportions.
(Adapted from Schaefer and Weber-Schöndorfer 2005).

1.4 Human teratogenesis

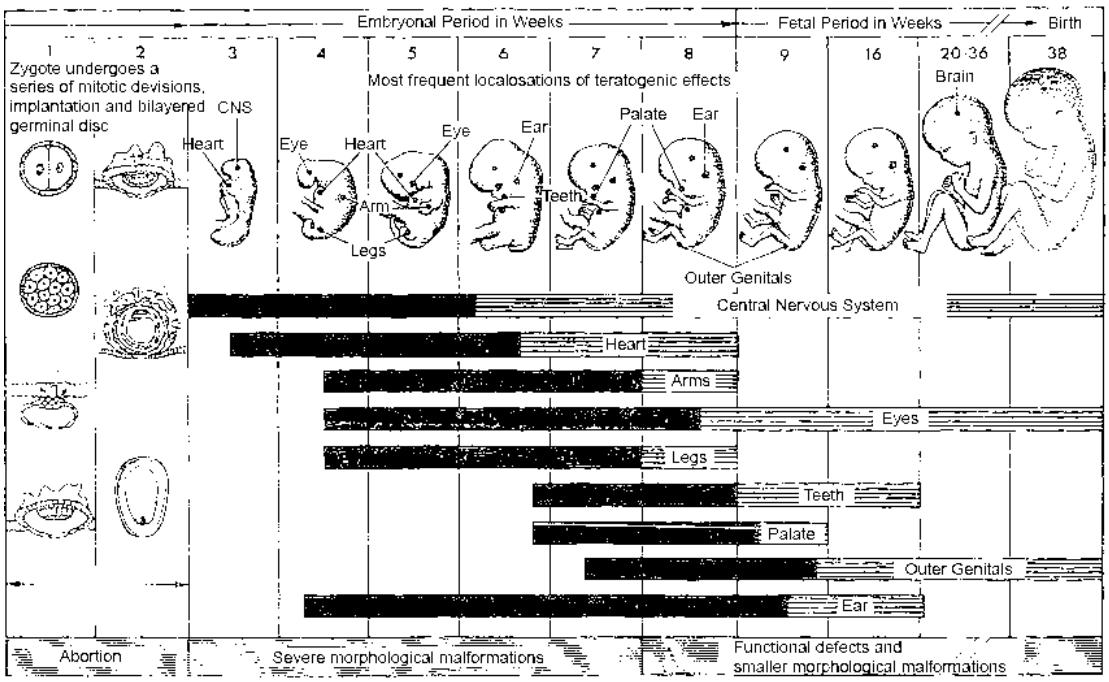
Teratogenesis is defined as the dysgenesis of fetal organs as evidenced either structurally or functionally (e.g. brain functions). The typical manifestations of teratogenesis are restricted growth or death of the fetus, carcinogenesis, and malformations, defined as defects on organ structure or function. These abnormalities vary in severity (e.g. hypospadias that is mild and may be missed, or is severe, necessitating several corrective operations). Major malformations may be life-threatening and require major surgery or may have serious cosmetic or functional effects (Koren et al. 1998).

1.5 Fundamentals of teratogenicity

Wilson (1977) stated six rules for embryotoxicity of medicinal products in humans basing on animal studies.

- Susceptibility of the embryo/fetus towards toxicological impact is depending upon the genotype. Variations in medicinal product response and toxicology between animals and humans are caused by different genomes. In addition, inter-individual genetic polymorphism in maternal or fetal genes may account for the variability in drug absorption, drug metabolism and drug excretion defects leading to deficiencies in drug-metabolizing enzymes, such as epioxidhydrolase in phenytoin metabolism (Depond et al. 2006; Mann and Pons 2007).
- Toxicological impact is depending on exposure to the medicinal product with respect to critical periods of susceptibility to the embryo. Within the first two weeks after conception until implantation, pluripotent cells can replace lost cells. Insults to the embryo lead to death or intact survival (“all or none period”). In this period agents cannot cause congenital malformations but embryolethality. During organogenesis (in humans day 15 to 60 post coitus) any damages are irreparable since this is the period of maximum sensitivity. Depending on the tissue medicinal products may cause congenital malformations.
  The fetal period (2nd and 3rd trimenon) is characterized by growth and functional maturation of organs and systems. In this period susceptibility decreases, but medicinal products may affect fetal growth and induce functional deficits as it has been shown for alcohol, lead and methylmercury, leading to intelligence deficits or renal impairment after exposure to angiotensin-converting-enzyme inhibitors (see also table 2).

Figure 1: Critical periods of embryo/fetal development



Particularly critical periods are shown in black, less sensitive periods are striped. (Adapted from Schaefer 2006)

- A number of embryotoxic compounds have relatively unspecific ways of affecting embryonal development, e.g. disturbance of CNS development caused by different medicinal products like carbamazepine, cyclophosphamide or warfarin.
- In general, the following courses of development are possible after a damage:
  - Standard development
    Especially in the first two weeks after conception, insults will be repaired. This may occur also in later developmental stages.
  - Death of the embryo or fetus before 20 weeks of gestation and spontaneous abortion
  - Death/stillbirth of the fetus after 20 weeks of gestation
  - Malformation of the embryo
  - Intrauterine retardation of growth
  - Disturbance of organ function
  - Transplacental carcinogenesis as has been proven in humans for diethylstilbestrol inducing vaginal carcinoma in female offspring (see also table 2).
- Transplacental transfer of a toxic agent is dependant on chemical and physical properties of the compound, e.g. its molecular size and low solubility limit its transplacental transfer (see above).
- Interference of embryonal development is proportional to the dose of toxic agent reaching the embryo/fetus. After exceeding a certain threshold, which is individual for each agent, initially an embryotoxic range is reached followed by embryoletal respective maternal toxic range.

2 Historical perspective

2.1 Thalidomide

For decades it was believed that the placenta served as a barrier that protects the fetus from the adverse effects of drugs (Koren et al. 1998). This opinion was drastically changed after the thalidomide tragedy. Approximately 10.000 children with severe limb defects and other organ dysgenesis (e.g. kidney and heart defects) were born between 1958 and 1961, whose mothers had taken the hypnotic and sedative drug thalidomide (Lenz 1961). The most striking feature was phocomelia – abnormally short limbs with flipper-like arms and toes sprouting from the hip. Despite the incidence of 20 to 30 percent of characteristic malformations, it required several years of thalidomide use before the cause-and-effect relationship between thalidomide in early pregnancy and its harmful effects was recognized. However, routine screening tests in rodents found thalidomide to be safe, and therefore its potent teratogenicity in humans and higher animals was not expected. Finally, in November 1961 thalidomide was withdrawn from the market.

The deformities caused by thalidomide were different, depending on the time of exposure during embryologic development. According to the days after conception, thalidomide causes anotia and duplication of the thumbs after exposure between days 20 to 24, phocomelia of the arms after exposure between days 24 to 33, phocomelia of the legs after exposure between days 28 to 33, and eye anomalies after exposure days 24 to 30 (Miller et al. 1999; Ward 2001).

Thalidomide is a racemic containing both left- and right-handed isomers in equal amounts. One enantiomer is effective against morning sickness, the other is teratogenic and causes birth defects. The enantiomers are converted to each other in vivo – that is, if a human is given (R)-thalidomide or (S)-thalidomide, both isomers can be found in the serum. Thus administering only one enantiomer will not prevent the teratogenic effect in humans (Eriksson et al. 1995; Eriksson et al. 2000).

The pharmacological basis for thalidomide's effect remains controversial. At the present time, the different mechanisms can be grouped into six categories, with thalidomide affecting Desoxyribonucleinacid (DNA) synthesis or transcription, growth factors, integrins, angiogenesis, chondrogenesis, cell death or cell injury (Trent and Fillimore 2000).
Against all expectations thalidomide is still used as pharmaceutical medication. Due to its anti-inflammatory effect it is administered to patients with erythema nodosum leprosum, a painful skin condition associated with leprosy, and its anti-angiogenic effect makes it attractive for the treatment of several types of cancer (Sales et al. 2007; Villahermosa et al. 2005; Durk 2006; Zustovich et al. 2007).

Since the 1960ies, pharmaceutical agents in pregnancy are applied with legitimate caution by physicians, pharmaceutical industry and patients. Most of the known human teratogenic medicinal products are associated with much lower rates of malformations, and the syndromes they cause are not always so obvious. This makes it difficult to confirm the causation. Case reports on malformations are available for numerous medicinal products but studies with statistical validity are often missing. More than 40 years after the recognition of thalidomide-associated embryopathy, fewer than 30 drugs have been proved to be teratogenic in humans when used in clinically effective doses (table 2) (Koren et al. 1998).

Table 2. Medicinal products with proven teratogenic effects in humans*

Medicinal product	Teratogenic effect
Aminopterin†, methotrexate	CNS and limb malformations
Angiotensin-converting-enzyme inhibitors	Prolonged renal failure in neonates, decreased skull ossification
Anticholinerge medicinal products (propylthiouracil and methimazole)	Neonatal meconium ileus
Carbamazepine	Neural-tube defects
Cyclophosphamide	CNS malformations, secondary cancer
Danazol and other androgenic medicinal products	Masculinization of the fetus
Diethylstilbestrol†	Vaginal carcinoma and other genitourinary defects
Hypoglycemic medicinal products	Neonatal hypoglycemia
Lithium	Ebstein's anomaly
Misoprostol	Moebius sequence
Nonsteroidal anti-inflammatory medicinal products	Constriction of the ductus arteriosus‡, necrotizing enterocolitis
Paramethadione†	Facial and CNS defects
Phenytoin	Growth retardation, CNS deficit
Psychoactive medicinal products (e.g. barbiturate, opioids, and benzodiazepine)	Neonatal withdrawal syndrome when medicinal product is taken in late pregnancy
Systemic retinoids (isotretinoin and etretinate)	CNS, craniofacial, cardiovascular and other defects
Tetracycline	Anomalies of teeth and bone
Thalidomide	Phocomelia, internal-organ defects
Trimethadione†	Facial and CNS defects
Valproic acid	Neural-tube defects
Warfarin	Skeletal and CNS defects, Dandy-Walker syndrome

*Only medicinal products that are teratogenic when used at clinically recommended doses are listed. The list includes all medicinal products proven to affect neonatal morphology or brain development, and some of the toxic manifestations predicted on the basis of the pharmacologic actions of the medicinal products. Data are from Briggs et al. 1994.

†The medicinal products is currently not in clinical use.

‡ Sulindac probably does not have this effect.

(Adapted from Koren et al. 1998)

2.2 Isotretinoin

After the thalidomide tragedy it was believed that appropriate labelling of teratogenic medicinal products would be effective to prevent fetal exposure to medicinal products. Reality showed that this was not the case. In the early 1980ies in North America isotretinoin, a known teratogenic drug in animals, was introduced in the market for the treatment of acne (Fantel et al. 1977; Kamm 1982). Shortly after it's approval, several publications appeared warning of the human teratogenic potential if isotretinoin was administered to women who were pregnant or who may become pregnant (Shalita et al. 1983). Despite explicit warning labels, many children with retinoid embryopathy were born in the years after the drug was introduced (Lammer et al. 1985). The reason was that women did not know that they were pregnant, in other cases the method of contraception failed or the women did not understand the warning since they were illiterate.

This experience led to the development of a more comprehensive prevention program concerning teratogenesis. This included detailed warning and line drawing of a malformed child and in addition, the women had to sign a consent paper to use two effective methods of birthcontrol (Pastuszak et al. 1994). After the implementation of the program in 1989, about 30 percent of the women with exposed fetuses did not use any mode of contraception, even though they were cognizant of the high fetal risk (Pastuszak et al. 1994).

2.3 Bendectin

The decision to accept the perception of teratogenic effects after medicinal product exposure must be made carefully. One example of premature acceptance may lead to false accusation resulting in withdrawal of the pharmaceutical from the market, as it was the case for Bendectin, a combination of an antihistamine and pyridoxine. Bendectin was used for treatment of nausea and vomiting during pregnancy in the USA in the late 1950ies and 1960ies. Despite prospective, cohort studies showing no teratogenic effect, studies with less robust designs, case-control studies with retrospective recall of drug intake, implicated it as teratogen (Holmes 1983; Brushwood 1983). Many lawsuits accusing Bendectin as teratogen caused the manufacturer to withdraw it from the market in 1982, leaving the physicians with limited alternatives to treat severe nausea and vomiting in pregnancy. Subsequently, doctors either chose not to treat nausea and vomiting or used other antiemetics that have not been as adequately studied (Ornstein et al. 1995). Against the expectation for a teratogenic drug estimated to have been taken by up to 40 percent of pregnant women, the rate of malformations did not decrease after the withdrawal of Bendectin (Ornstein et al. 1995). In Canada, a review committee has advised the Canadian Minister of Health that the drug is safe and thus Bendectin continues to be marketed under the trade name Diclectin (Ornstein et al. 1995).

Other commonly used medicinal products like salicylates, glucocorticoides and spermicides, initially thought to be teratogenic, were proved to be safe in subsequent, better controlled clinical trials (table 3).

Table 3. Medicinal products initially thought to be teratogenic, but were proved to be safe subsequently

Medicinal product	Initial supposed risk	Teratogenic effect
Diazepam*	Oral clefts (Saxen 1975)	No increased risk in large cohort and case-control studies (Rosenberg et al.1983; Shiono et al. 1984)
Oral contraceptives	Birth defects involving the vertebrae, anus, heart, trachea esophagus, kidney and limbs, masculinizing effects on female fetuses resulting in Pseudohermaphroditism (Nora et al. 1978; Schardein et al. 1980)	No association between first-trimester exposure to oral contraceptives and malformations in general or external genital malformations in two meta-analyses (Bracken 1990, Raman-Wilms et al. 1995)
Spermicides	Limb defects, tumors, Down's Syndrome and hypospadias (Jick et al. 1981)	No increase in risk in a meta-analyses (Einarson et al. 1990)
Salicylates	Cleft palade and congenital heart disease (Walker 1971)	No increase in risk in large cohort studies (Werler et al. 1989; Slone et al. 1976)
Bendictin (doxylamine plus pyridoxine)	Cardiac and limb defects (Dickson et al. 1977; Donnai et al. 1978)	No increase in risk two meta-analyses (Einarson et al. 1988; McKeigue et al. 1994)

*Diazepam taken near term may cause the neonatal withdrawal syndrome or cardiorespiratory instability.
(Adapted from Koren et al. 1998)

3 Current process to classify safety and risk of medicinal products in pregnant women

Due to missing or insufficient human data, government agencies and pharmaceutical industry are forced to label medicinal products with contraindications or at least "strict indication for use during pregnancy" which often causes physicians to restrict therapeutic regimen. Especially for expecting mothers with chronic diseases like bronchial asthma, psychiatric disorders, epilepsy, hypertension or autoimmune diseases, therapeutic nihilism may lead to a dramatic deterioration of the disease, and this may also induce a higher risk for the fetal development. On the other hand numerous abortions without profound indications are carried out due to insufficient information of patients and medical staff concerning the real risk of a medicinal product used during early pregnancy.

3.1 Assessing the risk for humans by means of animal studies

Before an investigational new medicinal product is allowed to be tested in human subjects certain preclinical animal studies must be completed, and further preclinical data are necessary before a marketing authorisation may be granted. The regulatory requirements in the European Community are laid down in the Annex of Directive 2001/83/EC[2], amended by Directive 2002/98/EC, Directive 2004/24/EC, Directive 2004/27/EC and Directive 2003/63/EC.

According to Directive 2003/63/EC the toxicological potential of a new medicinal product comprises a range of animal studies including single-dose toxicity, repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity (see below), the prove of local tolerance and if applicable phototoxicity. Other studies like immunotoxicity, antigenicity or studies on impurities must be considered case by case. The requirements of the studies are defined by various guidelines published by the EMEA (http://www.emea.eu.int/htms/human/humanguidelines/nonclinical.htm).
With regard to damages to the germ-line and/or the offspring after exposure to medicinal products Part I of Directive 2003/63/EC section c) Geno-toxicity states[3]:

"The purpose of the study of mutagenic and clastogenic potential is to reveal the changes which a substance may cause in the genetic material of individuals or cells. Mutagenic substances may present a hazard to health since exposure to a mutagen carries the risk of inducing germ-line mutation, with the possibility of inherited disorders, and the risk of somatic mutations including those leading to cancer. These studies are obligatory for any new substance."

The recommendations for testing strategies are laid down in the "Note for Guidance on specific regulatory genotoxicity tests for pharmaceuticals CPMP/ICH/141/95" (International Conference of Harmonisation [ICH] S2A) and "Note for Guidance on Gentoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals CPMP/ICH/174/95" (ICH S2B).

Comprehensive tests used to identify compounds with the risk of inducing genetic damages should include gene mutations, structural aberrations of chromosomes (clastogenicity) as well as recombination and numerical chromosome aberrations (aneupoloidy). Since no single test is able to provide the required information, a combination of tests (standard battery test) is recommended which may be adapted appropriately to the individual medicinal product and the information needed: (i) A test for gene mutation in bacteria. (ii) An in vitro test using mammalian cells with cytogenetic evaluation of chromosomal damage, or an in vitro mouse lymphoma thymidine kinase assay. (iii) An in vivo test using rodent hematopoietic cells to identify chromosomal damage.

ICH S2A Guidance addresses the evaluation of test results: Negative results of the three standard battery tests usually provide sufficient evidence for the absence of genotoxicity of a compound, provided that the tests were adapted where necessary. The interpretation of positive results in any assay for genotoxicity does not necessarily mean that the test compound poses a genotoxic/carcinogenic hazard to humans, since these tests were designed to optimize sensitivity at the expense of specificity to insure that all genotoxic compounds are identified. Therefore in vitro positive test results should be evaluated for their biological relevance assessing a number of conditions which may lead to a positive test result. The background that germ line mutations are clearly associated with human diseases,

[2] In the following text "2001/83/EC" refers to the amended version.
[3] Legislation texts are written in italic.

and the suspicion that a compound may induce heritable effects is considered to be just as serious as the suspicion that a compound may induce cancer.

In part I of Directive 2003/63/EC section e) Reproductive and developmental toxicity is laid down:

"Investigation of possible impairment of male or female reproductive function as well as harmful effects on progeny shall be performed by appropriate tests.

These tests comprise studies of effect on adult male or female reproductive function, studies of the toxic and teratogenic effects at all stages of development from conception to sexual maturity as well as latent effects, when the medicinal product under investigation has been administered to the female during pregnancy.

Omission of these tests must be adequately justified.

Depending on the indicated use of the medicinal product, additional studies addressing development when administering the medicinal product of the offspring may be warranted.

Embryo/fetal toxicity studies shall normally be conducted on two mammalian species, one of which shall be other than a rodent. Peri-and postnatal studies shall be conducted in at least one species. If the metabolism of a medicinal product in particular species is known to be similar to that in man, it is desirable to include this species. It is also desirable that one of the species is the same as in the repeated dose toxicity studies."

In general, studies of reproductive and developmental toxicology investigate possible impairment of male or female reproductive function as well as harmful effects on progeny and compare the outcome with untreated control animals or control animals treated with the vehicle, respectively. The recommendations on appropriate approaches for reproductive toxicology tests are provided by the Guidelines "Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility CPMP/ICH/386/95 and CPMP/ICH/136/95; ICH S5(R2)". For a chemical to be labelled developmental toxic it must significantly increase the occurrence of structural or functional abnormalities in the exposed offspring at a dose that does not cause severe toxicity in the mother. Doses causing severe maternal toxicity are not useful, since embryo/fetal adverse effects could be a direct consequence of the active substance or secondary to the poor maternal condition. The dose range tested should cover a minimal maternal toxicity as well as a no adverse effect dose. The exposure in pregnant animals should be measured by plasma concentrations of the compound and/or metabolites.

The investigations have to be done in two species: one rodent, preferably rats and one non-rodent, preferably rabbit. If the metabolism in another species is known to be similar to the human metabolism then this species should be included. The used animals must be well defined concerning health, fertility, fecundity, prevalence of abnormalities, embryo-fetal deaths and consistency being displayed within the different studies. Further the route of administration should be the same as the intended human usage, and one of the species should be same as in the repeated dose toxicity studies.

In order to detect immediate and latent effects of embryo/fetal toxicity, observations should comprise one complete life cycle from conception in parental generation (F_0) to conception in the offspring generation (F_1). The testing can be divided in the following stages:

- "*Premating to conception (adult male and female reproductive functions, development and maturation of gametes, mating behaviour, fertilisation).*
- *Conception to implantation (adult male and female reproductive functions, preimplantation development, implantation).*

- *Implantation to closure of the hard palate (adult male and female reproductive functions, embryonic development, major organ formation).*
- *Closure of the hard palate to the end of pregnancy (adult female reproductive functions, fetal development and growth, organ development and growth).*
- *Birth to weaning (adult female reproductive functions, neonate adaption to extrauterine life, pre-weaning development and growth).*
- *Weaning to sexual maturity (post-weaning development and growth, adaption to independent life, attainment of full sexual function).”*

3.1.1 Fertility and embryonic development

The objective is to detect toxic effects in the treated animals before mating through mating and implantation. Tests in females should comprise effects on oestrus cycle, tubal transport, implantation and development of pre-implantation of the embryo. Male testing should include histological examination of reproductive organs as well as testing of functional defects like libido and epididymal sperm maturation.

3.1.2 Embryofetal development

As already mentioned insults to the embryo during the period of conception and implantation may lead to death of the embryo or have no effect (“all or none period”). Due to the capability of omnipotent cells to replace lost or damaged cells congenital malformations are not observed but embryolethality is. Like in humans damages during organogenesis result in congenital malformations depending on the time of exposure and the differentiating tissue.

To observe any effect on the fetus in animal studies investigation at the terminal examination should include: macroscopic examination of all adults, histological evaluation of organs with macroscopic findings, number of corpora lutea, number of life and dead conceptuses and implantation sites, fetal body weight and abnormalities.

3.1.3 Prenatal and postnatal development including maternal function

Adverse effects of medicinal product exposure at late stages of pregnancy or in lactating period through weaning may affect the development of the conceptus and/or offspring. In order to detect delayed manifestations of toxic effects during this period, observations should continue through sexual maturity. Females are allowed to deliver and raise the offspring to weaning at which time one male and one female should be selected to raise to adulthood and reproduction. Investigations should comprise macroscopic examination of all adult animals, live and dead offspring at birth, peri- and postnatal survival, growth and physical development, functional development/deficits including behaviour, mating and reproduction of F_1 generation.

3.1.4 Juvenile animal studies

Testing in juvenile animals is considered to be helpful for assessing adverse effects in paediatric population, including possible medicinal product effects on developmental

processes. Therefore individual study designs involving treatment of offspring (at ages to be specified) should be deemed.

Although the animal tests are carefully conducted, government agencies, pharmaceutical industry and physicians are aware that there are limitations to the approach to predict human teratogenicity from animal studies. Thus results from animal studies cannot be uncritically extrapolated to humans. It is possible that positive animal studies may be irrelevant for humans, as it was shown for salicylates causing cardiac malformations in animals but not in humans (Wilson et al. 1977; Werler et al. 1989). Further, drugs may have teratogenic effects in animals when they are administered in high dosis that are not teratogenic in humans when given in clinically relevant doses (Enns et al. 1999). But also negative tests in animal studies do not absolutely prevent the medicinal product from causing serious problems in humans. Possible reasons for this discrepancy may be fundamentally different species-specific strategies for maternal-embryonic exchange during early pregnancy, other pharmacokinetic characteristics of the test compound, different characteristics of gestational physiology and periods of susceptibility (Carney et al. 2004; Schardein et al. 1985).

Several factors must be taken into account for the assessment of findings or the absence of effects:

- What is known about metabolism and pharmacokinetics in the species studied?
- Is the route of administration relevant?
- At which plasma concentrations are adverse effects/no effects observed?
- Are the observed adverse effects a class effect for all pharmacological substances of this type?
- What is the mechanism behind the observed adverse effects (e.g. maternal toxicity, evidence of direct embryo/fetotoxicity, death of offspring secondary to impaired maternal care)?
- Is the mechanism of relevance to humans (Sannerstedt et al. 1996)?

The conclusion that a medicinal product is associated with an increased risk for malformations in humans can only be drawn over time based signals which are subsequently confirmed after approval.

3.2 Human Pregnancy Data from Pre-Authorisation studies (Clinical trials)

3.2.1 Regulatory requirements for including women of childbearing potential

Due to the concern for the inadvertent exposure of an embryo/fetus, women of childbearing potential may be included in clinical trials only if certain requirements are accomplished. Currently regional differences in the timing of reproduction toxicity studies still exist between Japan, EU and USA. According to the “Guideline on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals; Reproduction toxicity studies; 9.3 Women of childbearing potential (CPMP/ICH/286/95)” it is required for

- women using effective birth control

  Japan: “*Assessment of female fertility and embryo-fetal development should be completed prior to the inclusion of women of childbearing potential using birth control in any type of clinical trial.”*

EU: *"Assessment of embryo-fetal development should be completed prior to Phase I trials in women of childbearing potential and female fertility studies prior to Phase III trials."*

USA: "*Women of childbearing potential may be included in early, carefully monitored studies without reproduction toxicity provided appropriate precautions are taken to minimize risk. These precautions include pregnancy testing and entry after a confirmed menstrual period. Continued testing and monitoring during the trial should be sufficient to ensure compliance with the measures not to become pregnant during the period of drug exposure (which may exceed the length of study). To support this approach, informed consent should include any known pertinent information related to reproductive toxicity, such as a general assessment of potential toxicity of pharmaceuticals with related structures or pharmaceutical effects. If no relevant information is available, the informed consent should clearly note the potential risk.*

In the 3 Regions, the pre- and post-natal development study should be submitted for marketing approval or earlier if there is cause of concern. For all regions, all female reproduction toxicity studies and the standard battery of genotoxicity tests should be completed prior to the inclusion, in any clinical trial, of women of childbearing potential not using highly effective birth control or whose pregnancy status is unknown."

- pregnant women or females whose pregnancy status is unknown
  Women of childbearing potential not using effective birth control or whose pregnancy status is not known are only allowed to be included in all 3 regions if the standard battery of genotoxicity tests and all female reproduction toxicity studies are completed.

  Pregnant women may be included into clinical research according to section 9.4 Pregnant women:

  "Prior to inclusion of pregnant women in clinical trials, all the reproduction toxicity studies and the standard battery of genotoxicity tests should be conducted. In addition, safety data from previous human exposure are generally needed."

In general, clinical trial program rarely includes pregnant women. Exceptions are if contraception failed in women of childbearing potential enrolled in the study. The restriction arises from concerns of possible teratogenic and future effects on the development of the fetus. Therefore studies are done on male and nonpregnant women leading to a lack of scientific knowledge of the clinical pharmacology, pharmacokinetics and pharmacodynamics of the medications administered during pregnancy.

3.3 Problems and difficulties to conduct clinical trials in pregnant women are multiple

Unless a product is intended specifically for use during pregnancy, pregnant women are excluded from clinical trials. Evaluating whether a new medicinal product is a significant human teratogen is in many ways more difficult than assessing other forms of toxicity.

3.3.1 Physiological changes during pregnancy

Responses to drugs are influenced by many factors including age, ethnic background, metabolic phenotype, body fat content and distribution, body size, the effect of hormones and concomitant therapies (Benet et al. 1984; Evans et al. 1986). In addition, physiological changes during pregnancy influence further features like absorption, distribution and clearance of the medicinal product (Table 4). Many of these changes can be observed in the first trimester of pregnancy, but the physiologic effects change throughout pregnancy and continue through the postpartum period.

Table 4. Physiological changes in pregnancy

- Cardiovascular system:
  50 % increase in plasma volume
  Increase in cardiac output
  Increased blood flow to uteroplacental unit
  Increased hepatic blood flow
- Respiratory system:
  Respiratory alkalosis
  Changes in lung volumes and capacities
- Changes in activity of enzyme systems involved in medicinal product metabolism
- Decrease in serum albumin filtration rate – leads to alteration in protein binding
- Increased glomerular filtration rate – leads to clearance changes
- Gastrointestinal system:
  Delayed gastric emptying
  Increased transit time
  Decreased stomach acidity

(Adapted from Fredericksen 2000)

Another important factor is the placental-fetal organ which is actively involved in the amount of drug crossing the placenta, the fraction of drug being metabolised by the placenta and the distribution and elimination of a drug by the fetus (Loebstein et al. 1997). In addition, also the specific characteristics of the drug substance like size, solubility, degree of ionization and molecular weight should be taken into consideration when predicting the time course of the drug concentration in the fetal-maternal unit (Loebsein et al. 1997). Last but not least, a teratogenic medicinal product usually causes malformations during a restricted period in early pregnancy, but may cause also fetal damages in the second or third trimester.

3.3.2 Ethical considerations

Pregnant women are classified as a vulnerable population requiring special protection. Therefore the legal and ethical issues in conducting clinical research in this population are very complex and may never be solved. The main barrier to include expecting mothers in clinical trials is the potential harm to mother, fetus or neonate. Clinical trials which are not well designed put the industry on extensive threat of litigation. Further, in wealthy countries as Germany, the existing health care systems ensure that expecting mothers have access to

medicinal progress and preventive pregnancy programs. Therefore the women are not forced to participate in clinical trials. A different situation is found in poor countries or at least in poor classes of societies (e.g. in USA or Africa) where the only way to get medicinal treatment is participating in clinical research programs.

3.3.3 Practicalities and logistics

The pregnant state is outstanding, and thus well designed study protocols are quite different from those developed for the nonpregnant women, since it is not possible to use laboratory tests as indicators for a graded response of adverse effects as can be done for potentially nephro- or hepatotoxic effects. Another aspect is that patient recruitment may be difficult resulting in a very long study period and/or an inadequate sample size of patients. Suppose that a specific birth defect occurs with an incidence of 1 per 1000 live birth. To prove that women who are taking the drug have twice the number of defective infants, a randomized, blinded clinical study would require approximately 18.500 treated women and the same number of untreated control subjects (Khouri et al. 1995). In addition some kind of malformations (e.g. cardiac, renal or intestinal malformation) may be not detected immediately at birth making it necessary to study adverse fetal and neonatal effects as long as possible up to several years. Due to a lack of guidelines and regulations promoting clinical studies in pregnant women government agencies, pharmaceutical industry and physicians are often in an insecure situation.

3.3.4 Clinical trials in pregnant women with severe chronic diseases

Despite the risk of teratogenicity, and even if the study protocols may not meet the standard of a randomized, prospective controlled trial, clinical drug research has been conducted in pregnant women with severe chronic diseases like seizure disorders (Barret and Richens 2003), psychiatric disorders (American Academy of Pediatrics, 2000), hypertension (Magee et al. 2000) or maternal infection with human immunodeficiency virus type 1 (HIV-1; Connor et al. 1994).

A multicenter clinical trial (Protocol 076) conducted by “The Pediatric AIDS Clinical Trial Group” demonstrated that zidovudine reduces the risk of the maternal-infant transmission of human immunodeficiency virus type 1 (HIV-1) by approximately two thirds (Connor et al. 1994). This randomized, double-blind, placebo-controlled trial enrolled untreated HIV-infected pregnant women, at 14-34 weeks’ gestation, which had CD4+ T-lymphocyte counts above 200 cells/mm^3 and no clinical indication for antenatal antiretroviral therapy. Zidovudine was given to the mother after the first trimester of pregnancy as well as during labor and delivery, and to the newborn for the first six weeks of life.

At the first interim analysis of efficacy, the “Data and Safety Monitoring Board” recommended that the enrolment of additional patients should be discontinued, and that all patients receiving a study drug in blinded fashion be offered zidovudine to reduce the risk of HIV-1 transmission (Connor et al. 1994). No incidence in growth, prematurity, or the number and pattern of major or minor congenital abnormalities were observed between the two groups. Thirty-three live born infants had congenital defects, 17 of 206 (8,3 %) in the treatment group and 16 of 209 (7,7 %) in the nontreated controls. The total incidence of malformations is higher than expected in the general population, but this probably reflects the population studied (Briggs et al. 2005). Among infants, the only short-term toxic effect direct attributable

to zidovudine was a decrease in hemoglobin concentration, which was mild and reversible (Connor et al. 1994). Although zidovudine appeared to be effective in reducing transmission of HIV-1 to the fetus, some infants became infected despite of treatment. Possible reasons proposed for these failures include (i) virus transmission before treatment, (ii) ineffective suppression of maternal viral replication, (iii) poor maternal compliance with the drug regimen, and (iv) virus resistance to zidovudine (Connor et al. 1994).

In current clinical practice this regimen combined with the waiver of breastfeeding is the standard care program to reduce the risk of vertical transmission of HIV infection in North-America, Europe and other countries.

3.4 The need to collect post-authorisation data

Normally a clinical trial program does not include pregnant women. When a new medicinal product is approved the only available data are based on animal studies resulting in a restricted labelling with contraindication, special warnings and strictly benefit/risk assessment.

The first hints referring to the association of medicinal product exposure and adverse fetal outcomes are published case reports. If the medicinal product in question has a strong teratogenic potential or causes rare malformation then a reasonable suspicion arises early. The teratogenicity of isotretinoin (Rosa 1983; Shalita et al. 1983) and warfarin (Barr and Burti 1976; Saxen 1975) were established on the basis of case reports. If, on the other hand, the drug is taken by many pregnant women (e.g. Bendectin), a small number of case reports of abnormalities may simply reflect the spontaneous occurrence of malformations in the general population, which ranges from 1 to 5 percent, unless there is a characteristic pattern of malformations (as, for example, with alcohol or thalidomide) (Koren et al. 1998).

To determine the relationship between exposure to a medicinal product and fetal outcome the collection of post-authorisation data is needed. Specific recommendations and instructions for surveillance are given in the “Guideline on the Exposure to Medicinal Products During Pregnancy: Need for Post-Authorisation Data (EMEA/CHMP/313666/2005)”.

The scope of the guideline is to provide criteria for which medicinal products active surveillance for collecting post-authorisation data in pregnancy is necessary, how to monitor accidental or intended exposure of pregnant women to medicinal products and specific requirements for reporting the collected data.

The group of medicinal products for which special surveillance during pregnancy is needed should be identified according to the following criteria:

- *“**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 posed 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, 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 constipation, fatigue, mild to moderate forms of allergic symptoms, common cold and others.*

  Safety concerns emphasise the need for data collection on exposure during pregnancy and the importance of pregnancy databases in revealing potential teratogenic/embryo-fetotoxic signals. On the other hand, medicinal products for which well-conducted epidemiological studies in pregnant women failed to demonstrate a risk to the fetus may be exempted.

- *Treatment to a **drug belonging to a class of substances** having a similar chemical structure or mechanism of action to:*
  - ***Suspected teratogenic, embryotoxic, fetotoxic or mutagenic effects** from **case reports** and **animal studies**;*
  - *Substances of which the **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 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)."*

In general, if one or several criteria above-mentioned apply to the medicinal product, the responsible marketing authorisation holder (MAH) is obliged to introduce a pro-active monitoring. In the safety specifications the MAH has to describe a summary of the identified and potential risks of the medicinal product as well as missing information for pregnancy in accordance to "Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03)" and "Guideline on Risk Management Systems for Medicinal Products for Human Use (EMEA/CHMP/96268/2005)". Further, the MAH must state which specific actions will be taken for risk management and on what basis these actions will be reported. Recommendations concerning the quality of collected data include:

- Exposure data specifying time periods of the pregnancy, dose and duration of administration.
- Outcome data which comprise structural malformations (mostly detected in the neonatal period) and non-structural or long-term functional effects which may be difficult to identify. It is recommended to follow-up the development of the newborn as long as possible and appropriate since some kind of malformations (e.g. cardiac, or intestinal malformations) may be not diagnosed immediately postpartum. In addition, data collection should also include autopsy results of stillbirths and, if possible,

examinations of the fetus after spontaneous or induced abortion. To provide reliable data it is recommended that examination should be conducted by a group of professionals, ideally including a paediatrician following a specific protocol. Another important point is to include also "normal" outcomes with information on exposure times.

Regardless of the procedure of authorisation, the MAH has to report the collected data on any adverse outcome, defined as physical defects or significant functional disturbance, after exposure during pregnancy for all medicinal products. This includes also case reports, cases from pre- and post-authorisation studies as well as data originating from worldwide literature.

The minimum required data for reports of adverse outcomes and data on exposure during pregnancy irrespective with or without adverse drug reaction (ADR) are similar to those required for any ADR: identifiable patient, identifiable reporter, suspected ADR and suspected medicinal product. For the reasons of standardised information, it is recommended to use a structured questionnaire to collect the following data (the guideline provides a list of data elements in annex 1):

- *"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).

  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 fetal 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, coadministered medicinal product), familial history of congenital anomaly etc.*
- *The results of examinations performed: fetal ultrasound, amniocentesis, laboratory tests, etc."*

To get all information available, 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 fetal autopsy and prenatal tests (e.g. ultrasound, amniocentesis, serum markers).*

- *For cases of **late fetal 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 fetal 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 fetotoxic 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."*

The importance of data on the exposure and subsequent outcome of pregnancy is emphasised since the MAH is requested to follow up cases of congenital malformations as long as possible to provide information on the final diagnosis, the severity and intended therapy (e.g. planned surgery).

According to Article 104 of Directive 2001/83/EC, Article 24 of Regulation EC 724/2004 for authorisations via the centralised procedure and Notice to Applicants (NTA; see chapter Vol 9A of the Rules Governing Medicinal Products in the European Union) the MAH has to submit expedited reports on ADR immediately and in no case later than 15 calendar days. This includes

- *"Reports of congenital anomaly(ies) in fetus, child*
- *Reports of late 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 hospitalisation."*

The reports have to be submitted electronically using the format recommended in the "Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03)" through the EudraVigilance system which includes a specific section for parent-child/fetus reports. In addition, annex 2 provides specific recommendations for the transmission of Individual Case Safety Reports (ICSR) of pregnancy exposure.
The MAH has to report positive and negative experiences during pregnancy in the Periodic Safety Update Reports (PSUR) pursuant to ICH E2C guideline and NTA Vol 9. The used sources can be case reports (analysed separately from studies and registries, differentiated whether prospective or retrospective cases), epidemiologic studies and data from pregnancy registries (external or internal).

The limitation of this approach is that first of all the physician or the pregnant woman must report any medicinal product exposure. This takes place more or less only after an adverse outcome of pregnancy or if there is an exaggerated perception of fetal risk considering the women to terminate the pregnancy. If at all, probably only a few cases of medicinal product exposure with normal outcome will be submitted voluntarily to the MAH.

3.5 Assessment of potential risk and conclusion

A decision scheme for integration of non-clinical and, if available, clinical data to assess the risk of an adverse reproductive/developmental effect in humans, and recommendations how to communicate the identified risk is provided in the "Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: From Data to Labelling (EMEA/CHMP/203927/2005)".

The legal basis is Directive 2001/83/EC. The guideline refers for non-clinical data to the guidelines on Reproductive Toxicity ("Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility" CPMP/ICH/386/95 and CPMP/ICH/136/95; ICH S5[R2]).

Applications for medicinal products claiming well-established use and mixed applications should be considered in accordance with the guideline on "Non-Clinical Documentation for Mixed Marketing Authorisation Applications (CPMP/SWP/799/95)" and the draft guideline "Non-Clinical Documentation for Herbal Medicinal Products in Applications for Marketing Authorisation (Bibliographical and mixed applications)" and "Applications for Simplified Registration (EMEA/HMPC/32116/05)".

In addition, clinical data should also be considered in the framework of the "Note for Guidance on the Exposure to Medicinal Products During Pregnancy: Need for Post-Authorisation Data (EMEA/CHMP/313666/2005)".

3.5.1 Assessment of non-clinical data

In the "Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: From Data to Labelling" is emphasised that the risk assessment should be based on clinical data, if sufficient relevant human data are available. For this reason all feasible sources shall be used, e.g. case-reports, epidemiological studies, pregnancy registries or teratogenic effects network. Animal data are only necessary, if human data are lacking or not sufficient. The evaluation process of observed effects in non-clinical studies should take into account: Data with respect to fertility, concordance in cross-species, type and multiplicity of effects, various stages of the reproduction process, frequency of observed effect (rare events), magnitude of adverse effect in the offspring versus maternal toxicity, comparison of the toxic and pharmacodynamic effective dosages (e.g. No Observed Adverse Effect Level; NOAEL) and animal to human exposure ratio (exposure of the animal at the NOAEL versus exposure of human at the maximum therapeutic dose).

3.5.2 Assessment of clinical data

According to the "Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: From Data to Labelling" the assessment of clinical data *"should take the methodology in account, including the quality of data, the existence of a non-exposed group or control group, the type of controls, and if possible, the inclusion of fetuses aborted due to malformation, etc. Parameters such as therapeutic benefit, therapeutic alternatives, clinical practices, pharmacokinetics, extraction procedure of herbal medicinal products, etc. should be considered."*

The exposure to a medicinal product during pregnancy may produce three major types of effects, depending on the period of interference in the development phase:

- *"A **teratogenic (malformative) effect**, associated with exposure at the beginning of pregnancy (the first trimester of pregnancy is the period of highest risk).*
- *A **fetotoxic effect**, which includes effects such as growth retardation or either histological or functional maturation of organs (the period of highest risk begins during the second trimester of pregnancy and continues throughout pregnancy). It needs to be considered that some effects on the offspring may not be detectable until later in life.*
- *A **pharmacological effect in the neonate**, which is mostly associated with an exposure at the end of pregnancy or during labour. The endpoint differs from the endpoint 'teratogenicity or fetotoxicity' although all endpoints could be caused by the pharmacology of the active substance."*

3.5.3 Assessment of a malformative effect

Since structural birth defects occur in approximately 3 to 5 % of all live births, consequently each individual type of rare malformation has an incidence of 1/1000 live births. The detection of malformations after exposure to a medicinal product is depending on the number of prospectively monitored pregnancies, resulting in different levels of certainty regarding the potential risk.

- Up to 300 pregnancies monitored (no or very limited data). From a statistical point of view a conclusion might be reached that the medicinal product is not responsible for a more than 10-fold increase of the overall frequency of malformations.
- Between 300 and 1000 pregnancies monitored (a limited number of data). A conclusion can be drawn that the risk is not more than 2-fold increased.
- An extensive number of data (not quantifiable beforehand) is needed to conclude that there is no risk.

A malformative effect is demonstrated, if there is clear evidence that a medicinal product is associated with the increase of the global rate of specific malformation. This can only be concluded on time based signals which need to be confirmed subsequently. A suggested or suspected malformation risk is based on several case-reports with a possible relationship between the medicinal product and the malformation, or studies suggest an increase in the overall frequency of malformations. The evidence of "no risk" associated with an active substance is based on reliable safety update reporting and/or literature data. An extensive number of high quality data is necessary to demonstrate this statement, preferably prospective data. This important information should be submitted to physicians and patients.

3.5.4 Administration during lactation

The "Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: From Data to Labelling" recommends for risk assessment of a medicinal product to mothers during lactation to use (i) non-clinical data and if available on (ii) clinical data. Important is that clinical data, when available, supersedes non-clinical data.

(i) Non-clinical data include: "*Transfer into milk, development of breastfed pups and physicochemical and PK characteristics of the active substance, supposed to estimate."*

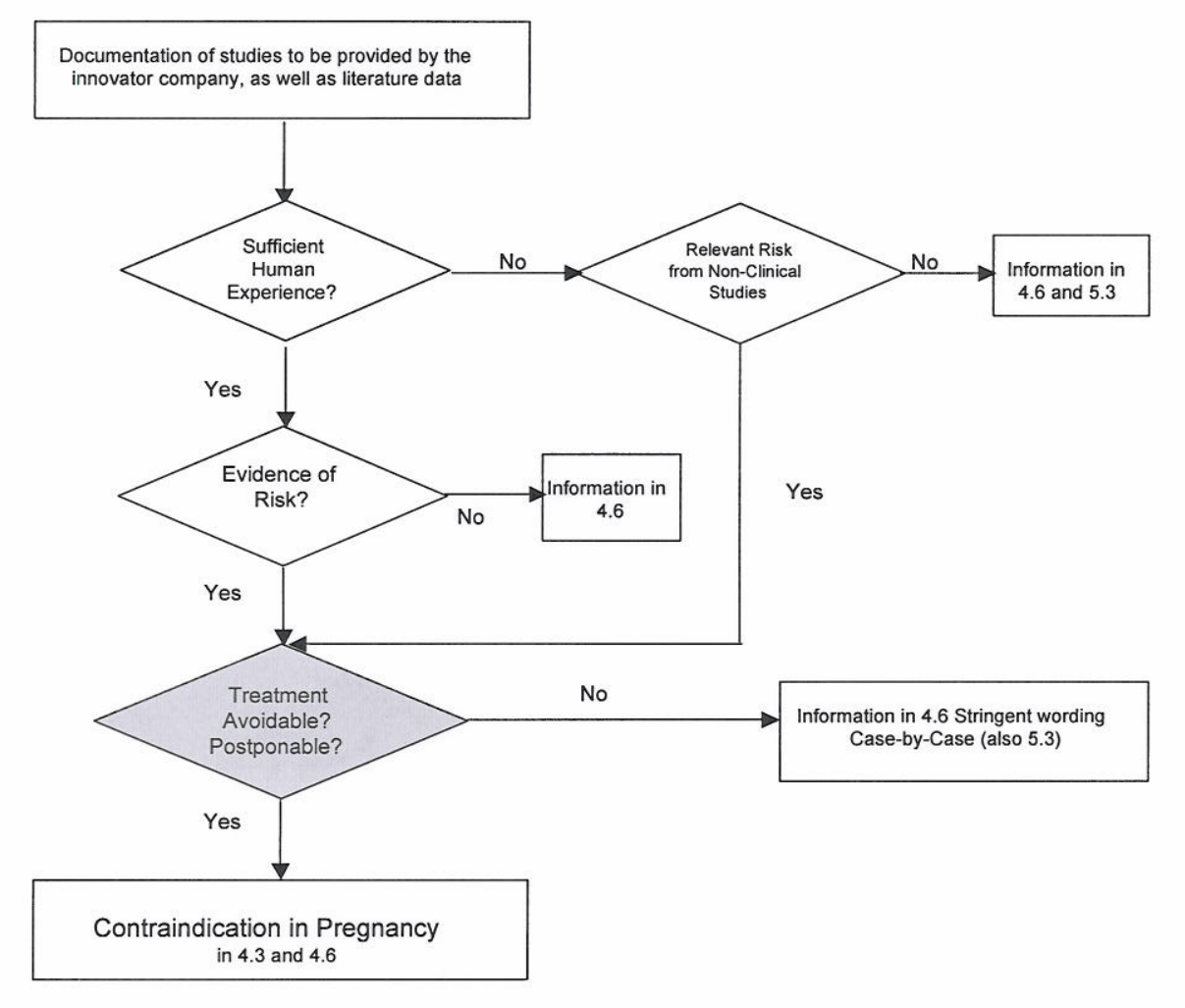
(ii) Clinical data take into account: *"Evidence of the milk transfer through analyses of human milk samples, follow-up of breastfed infants of treated mothers, adverse events reported in breastfed infants and related to maternal intake, is the medicinal product usually administered to neonates or not?"*

3.5.5 Conclusion of indicated risk

A contraindication ("absolute contraindication" or "strict contraindication") in pregnancy and/or a strict warning not to become pregnant must be mentioned if the risk to the developing embryo/fetus significantly outweighs the potential benefit to the mother or the unborn child. This must be stated in section 4.3 (Contraindications) of the SmPC, and a cross-reference should be given in section 4.6 (Pregnancy and Lactation). The decision whether a contraindication in pregnancy is necessary (figure 2) should be based on (i) human experience, (ii) relevant non-clinical studies and(iii) the need for treatment.

(i) Where there is sufficient experience in humans and the conclusion that no risk exists should be indicated in section 4.6. (ii) In cases where the clinical data are insufficient or not available, the risk assessment must rely on the findings of reliable animal studies. Section 4.6 must always refer to section 5.3 (Preclinical safety data) where the relevant non-clinical data should be provided. (iii) If there is a potential risk to the developing embryo/fetus after exposure to the medicinal product, then the risk must be weight against the potential benefit, before the conclusion of a contraindication is drawn. It should be taken into account if the disease is life threatening, whether there is an option of alternative and safer treatment and whether the possibility to modify, defer or avoid the treatment. In cases where there is no alternative and safer treatment, and treatment cannot be delayed, the product should not be contraindicated in pregnancy.

Figure 2. Decision scheme contraindication in pregnancy



A contraindication in pregnancy must be mentioned in the SmPC in section 4.3. A cross-reference should also be given in section 4.6 Pregnancy and lactation.

(Adapted from Appendix 2, "Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: From Data to Labelling [EMEA/CHMP/203927/2005]").

3.6 Labelling of medicinal product appropriate to the identified risk

The identified risks have to be reflected in the labelling of the medicinal product. Labelling includes the Summary of Product Characteristic (SmPC), the package leaflet, as well as the label on the immediate packaging and on the outside container. In general, a comprehensive labelling summarises all available data about the risk and benefit associated with the medicinal product, enabling the prescribing physician and the patient to decide in favour of the best treatment.

3.6.1 Summary of Product Characteristics

According to Article 8(3)(j) of Directive 2001/83/EC and Article 6(1) of Regulation 726/2004, every marketing authorisation application (MAA) requires beside other documents a SmPC. The content of the SmPC is governed by Article 11 of Directive 2001/83/EC, the Community

Code on human medicinal products. It provides the basic information about safety and efficacy of the medicinal product as it is agreed between the competent authority and the MAH. The “Guideline on Summary of Product Characteristics” of NTA Vol 2C gives detailed information about the content, necessary elements and the structure of the document.

In section 4.6 Use during pregnancy and lactation information has to be provided with respect of (i) fertility, (ii) pregnancy, (iii) lactation and (iv) women of child-bearing potential/contraception.

(i) Fertility: Concerning fertility, the main information on the possible effects on the medicinal product should be provided in section 4.6 and, if appropriate, cross-reference may be included in section 4.3. In cases where no human data are available, no wording on fertility is necessary. If relevant, the lack of non-clinical data should be provided in section 5.3.

(ii) Pregnancy: With respect to pregnancy, only conclusions of non-clinical reproductive studies which are relevant for the assessment of the risk are provided in section 4.6, further details should be given in section 5.3. If a medicinal product is known to be teratogenic or non teratogenic in humans, then non-clinical data should not be mentioned. The section should provide the extent of human experience, comprehensive information on clinical data (relevant adverse events reported on the embryo, fetus, infant and pregnant woman) and the frequency of such events. Further, recommendations should be given on the use of the medicinal product during the different periods of gestation, and the management of exposure including monitoring. Cross-references may be included in section 4.4 Special warnings and precautions for use as well as section 4.8 Undesirable effects.

If a medicinal product is strictly contraindicated during pregnancy, since the risk to the pregnant woman or the fetal/unborn child significantly outweighs the potential benefit, it must be mentioned in section 4.3 Contraindication.

(iii) Lactation: If available, in this section should be mentioned whether the active substance and/or its metabolite(s) is excreted in human milk (positive/negative excretion, milk/serum ratio) and provide information on adverse events in nursing neonates/infants. Recommendation should be given to stop or continue breastfeeding and/or treatment. Topical application on the breast should be considered according to the direct risk for the newborn. Non-clinical data are only relevant, if no human data are available.

(iv) Women of childbearing potential/contraception: Recommendations on the use of the medicinal product in women of childbearing potential should be provided when relevant. This should include pregnancy tests and contraception. In section 4.6 of the SmPC should be mentioned if an efficient contraception is required for the patient or her partner during treatment and for a defined period after ending treatment.

The guideline provide examples of the wording for the section pregnancy in Annex I (currently under review) and for the section lactation in Annex 3.

3.6.2 Package leaflet and labelling

The provisions concerning labelling of the outer and immediate packaging of medicinal products and the content of the package leaflet are laid down in Title V, Articles 54 to 69 of Directive 2001/83/EC. Article 59 of Directive 2001/83/EC states that the content of the package leaflet has to be drawn in accordance to the SmPC. Therefore all information given in the SmPC must also be presented to the patients. Pursuant to Article 62 of Directive 2001/83/EC the outer packaging and the package leaflet may include symbols or pictograms

designed in order to clarify information mentioned in the particulars or other information contained in the SmPC.

As it has been shown for teratogenic medicinal products like isotretinoin, pictograms or symbols may be helpful to inform women, especially if women do not understand the warning since they are illiterate.

3.7 Risk classification systems of different countries

In 1978, the first drug safety classification system concerning fetal safety was introduced in Sweden (FASS, 1993) followed by the USA one year later (Briggs et al. 1994). The classification systems are based on data from human and animal studies to provide information to health care professionals about possible and established risks or safety of using drugs during pregnancy and lactation (Addis et al. 2000; Alvan et al. 1995; Doering et al. 2002). The Swedish System of Approved Drugs (FASS) comprises four categories, A to D, in which B is divided in another 3 subgroups (table 5). Category A indicates the safest medicinal products, category D is used for medicinal products which are suspected or proven to cause malformations to the fetus. In the Swedish System not all drugs are classified e. g. vitamins, drugs used to induce abortions, drugs intended only to be used by males, plasma substitutes and solutions for infusion, as well as most preparations intended for topical use (Sannerstedt et al. 1996).

The FDA classification contains the categories A to D and in addition an X category for medicinal products demonstrated to be teratogenic (table 5). The Swedish system of risk stratification has proven over the years to have greater utility than the US system, since in Sweden the categories are subject to continuous follow-up by a multidisciplinary panel of experts (Sannerstedt et al. 1996; Uhl et al. 2002). Based on registry data, retrospective chart review, and postmarketing surveillance in humans, medications can move from one category to another. For example, in the Swedish system antipsychotics and benzodiazepines were both moved from category A to C in the 1980s, because they can interfere with neonatal adaptation (Sannerstedt et al. 1996).

The classification system adopted by the Australian Drug Evaluation Committee (ADEC 1992) is only slightly modified from the Swedish system, except that it uses a category X (Addis et al. 2000) (table 5).

Table 5. Definitions for the risk categories of FASS, FDA and ADEC

FASS (Sweden)	
Category A*	Drugs which have been taken by a large number of pregnant women and women of child-bearing age without any identified disturbance in the reproductive process, e.g. an increased incidence of malformations or other direct or indirect harmful effects. Due to extensive experience in humans, no regard is paid to animal data even if they show harmful effects on the fetus or on the reproductive process.
Category B	Drugs which may be assumed to have been used only by a limited number of pregnant women and women of child-bearing age, without any identified disturbance in the reproductive process having been

	noted so far, e.g. an increased incidence of malformations or other direct or indirect harmful effects on the fetus. As experience of effects of drugs in man is limited in this category, results of reproduction toxicity studies in animals are indicated by allocation to one of three subgroups B1, B2 or B3 according to the following definitions:
Category B1*	Reproduction toxicity studies have not given evidence of an increased incidence of fetal damage.
Category B2*	Reproduction toxicity studies are inadequate and may be lacking, but available data show no evidence of an increased occurrence of fetal damage or deleterious effects on the reproductive process.
Category B3†	Reproduction toxicity studies have revealed an increased incidence of fetal damage or other deleterious effects on the reproductive process, the significance of which is considered uncertain in humans. This subgroup is only used for new drugs with registered reproduction toxicity in animals and when it is unclear whether this effect is of relevance for humans.
Category C†	Drugs by which their pharmacological effects have caused, or must be suspected of causing, disturbances in the reproduction process that may involve risk to the fetus without being directly teratogenic. If experimental studies in animals have indicated an increased occurrence of fetal injuries or other disturbances of the reproductive process of uncertain insignificance in humans, these findings are to be stated for drugs in this category.
Category D‡	Drugs which have caused an increased incidence of fetal malformations or other permanent damage in humans, or which, on the basis of e.g. reproduction toxicity studies, must be suspected of doing so.
FDA (USA)	
Category A*	Controlled studies show no risk. Adequate, well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus.
Category B†	Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal-reproduction studies have shown an adverse effects that was not confirmed in controlled studies in women.
Category C†	Either animal-reproduction studies have revealed adverse effects on the fetus and there are no controlled studies in women, or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.
Category D‡	There is positive evidence of fetal risk, but the benefit from the use in pregnant women may be acceptable despite the risk (e.g. if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
Category X‡	Studies in animals or humans demonstrated fetal abnormalities, or there is evidence, or both, and the risk of the use of the drug in

	pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.
ADEC (Australia)	
Category A - D	A*; B1*, B2*, B3†, C†, D‡ similar to the FASS definitions.
Category X†	Drugs that have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy.

*Drugs grouped as probably safe.
†Drugs grouped as potentially harmful.
‡Drugs grouped as clearly harmful.

A risk factor category allocation for 645 drugs classified by the FDA, 446 classified by ADEC and 527 classified by FASS revealed that only 61 (26 %) of the 236 drugs common to all 3 systems are assigned to the same risk category (3 assigned to category A, 13 to B, 30 to C and 15 to D) (Addis et al. 2000). While 26 % of the drugs in Sweden are classified as category A, only 0,7 % of the drugs marketed in the US are in FDA category A (Sannerstedt et al. 1996). FDA uses the label category A only where controlled clinical data show no risk. Despite the more restrictive requirements of the FDA system, retinol (vitamin A), classified as safe for use in pregnancy by the FDA, is considered potentially teratogenic (Category D) by ADEC and FASS (Addis et al. 2000). Eight of the drugs found in all 3 classifications, are labelled with an X risk factor (teratogenic) by the FDA. Of these, 3 are classified as safe (B or A) by ADEC or FASS (Addis et al. 2000). An analysis of the three classification systems revealed the differences are not only based on the different criteria for assignment, but also due to how the original data sources are interpreted (Addis et al. 2000).

In 1987, the Netherlands adopted the Swedish pregnancy classification system and included a category X according to the Australian definition. Denmark introduced its own system, consisting of 5 standardised phases whether a medicinal product can be given or should be avoided during pregnancy in 1991. Switzerland adopted the US system in its “Kompendium der Schweiz”.

The pregnancy risk classification system of Germany comprises 11 categories (table 6) published in the medicinal product compendium “Rote Liste”.

Table 6. Definitions for the German pregnancy risk categories

Category 1	Medicinal products were taken by a large number of humans with no incidence of harmful effects on the embryo or fetus. In addition, animal studies show no incidence of embryotoxic/fetotoxic effects.
Category 2	Medicinal products were taken by a large number of humans with no incidence of harmful effects on the embryo or fetus.
Category 3	Medicinal products were taken by a large number of humans with no incidence of harmful effects on the embryo or fetus. Animal studies show incidence of embryotoxic/fetotoxic effects. This seems to be of no significance for humans.

Category 4	No sufficient data are available for use in humans. Animal studies show no incidence of embryotoxic/fetotoxic effects.
Category 5	No sufficient data are available for use in humans.
Category 6	No sufficient data are available for use in humans. Animal studies show incidence of embryotoxic/fetotoxic effects.
Category 7	Positive evidence of embryotoxic/fetotoxic risk in humans (first trimenon).
Category 8	Positive evidence of risk to the fetus in humans (second and third trimenon).
Category 9	Medicinal products causing an increased risk of perinatal complications or damages in humans.
Category 10	Medicinal products causing an increased risk of hormone-specific adverse effects on the fetus or neonate in humans.
Category 11	Medicinal products causing an increased risk of mutagenic/cancerogenic effects.

Categories 1 to 3 include medicinal products that are expected to be secure with all known odds, which have been taken by a large number of pregnant women without an increased incidence of malformations or other harmful effects on the embryo. However, medicinal products should be given during pregnancy, especially within the first trimenon, with caution and strictly indicated. The potential risk for mother and fetus should be taken into account. Medicinal products in category 4 to 6 are assumed to have been used only by a limited number of pregnant women, without an increased incidence of malformation or other severe adverse effects on the embryo. This includes medicinal products which have been available only for a short time, and medicinal products which are indicated only for a limited number of pregnant women. Most of the medicinal products belong to these classifications. “Embryotoxic effect” in category 7 is defined as direct or indirect effect on the fetus lasting temporary or remaining. Category 8 “fetotoxic effect” is defined as direct or indirect effect on the fetus lasting temporary (e.g electrolyte disturbance after taking diuretic medicinal products) or remaining (e.g. teeth discolouration after tetracycline use). Category 9 includes medicinal products causing “perinatal complications or damages”, which means medicinal products effects influencing parturition (e.g. uterus contraction or bleeding) or effects on the fetus or newborn (e.g. icterus neonatorum). Category 10 comprises exclusively effects caused by sexual hormones such as masculinizing effects on female fetus.

Even if the German classification system is published in the medicinal product compendium “Rote Liste” it is not of relevance for the current labelling of medicinal products. On the other hand, despite the efforts made by the European Union in the last 15 years, so far no common European risk classification system has been established.
Despite of a vast variety of regional attempts it becomes apparent that there is still a long way before a standardized classification system will be obtained.

3.8 Pharmacovigilance activities

Article 6 of Regulation (EC) No 726/2004 and Article 8 of Directive 2001/83/EC lay down the particulars and documents to be included in an application for the authorisation of a medicinal product for human use. According to Article 8 Directive 2001/83/EC , para 3. “*The*

application shall be accompanied by the following particulars and documents, submitted in accordance with Annex I:

… (ia) A detailed description of the pharmacovigilance and, where appropriate, of the risk management system which the applicant will introduce.

… (n) Proof that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country."

It should be noted, that the pharmacovigilance requirements apply to all medicinal products authorised in the EU irrespective of the procedure used for their authorisation.

Recently new pharmacovigilance guidelines have been developed in the course of ICH: The "Guideline on Risk Management Systems for Medicinal Products for Human Use (EMEA/CHMP/96268/2005)" and the "Note for Guidance on Planning Pharmacovigilance Activities (CHMP/ICH/5716/03)". Both guidelines are included in NTA, chapter "Volume 9A of The Rules Governing Medicinal Products in the European Union", which summarises the European provisions concerning pharmacovigilance for medicinal products for use in humans.

3.8.1 Risk Management System

In the "Guideline on Risk Management Systems for Medicinal Products for Human Use" a Risk Management System is defined as "*a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products, and the assessment of the effectiveness of those interventions."*

The description of a Risk Management System has to be submitted in the form of an EU-Risk Management Plan (EU-RMP), containing two parts:

- Part 1 includes a Safety Specification and a Pharmacovigilance Plan;
- Part 2 comprises an evaluation of the need for risk minimisation activities, which can be divided in routine activities and, if needed, additional activities. In case of additional risk minimisation activities, the applicant/MAH should establish a risk minimisation plan and provide it within Part 2.

3.8.2 Safety Specifications

In the "Guideline on Risk Management Systems for Medicinal Products for Human Use" and "Volume 9A of The Rules Governing Medicinal Products in the European Union" Safety Specifications are defined as *"a summary of the important identified risks of a drug, important potential risks, and important missing information. It should also address the populations potentially at-risk (where the product is likely to be used), and outstanding safety questions which warrant further investigation to refine understanding of the benefit-risk profile during the postauthorisation period. The Safety Specification is intended to help industry and regulators identify any need for specific data collection and also to facilitate the construction of the Pharmacovigilance Plan.*

In the EU-RMP the Safety Specification will also form the basis of the evaluation of the need for risk minimisation activities and, where appropriate, the risk minimisation plan."

In addition, it should be specified which populations have not been studied or have been studied to a limited degree in the pre-authorisation phase (e.g. children and pregnant or lactating women). More information should be given on identified and potential risks that require further evaluation as well as important missing information.

3.8.3 Pharmacovigilance Plan

According to ICH E2E the applicant or MAH should provide a Pharmacovigilance Plan based on Safety Specification (important identified and potential risks, missing information). The Pharmacovigilance Plan should propose risk minimisation activities to address the safety concerns identified in the specification. It should reveal missing pre-approval data and propose the required data which should be collected post-approval. The Pharmacovigilance Plan will deal with the issue of drug exposure during pregnancy – intended or not – and whether there is a need of appropriate activities.

It is recommended to use the Pharmacovigilance Plan as a document for early discussion between the competent authorities and the applicant or MAH.

3.8.4 Risk Minimisation Activities

In order to choose appropriate methods of risk minimisation activities, the applicant or MAH will take into account the indication, the population to be treated and the extent of missing data on a case by case basis.

A possible plan for a known teratogen like isotretinoin for the treatment of acne may have the following objectives:

- Effective contraception, and the need for a pregnancy test before each prescription.
- Additional educational material to the physician and the patient concerning the risks of the medicinal product and the need for contraception. Depending on the specific safety concern, the choice of media and the used educational material may include a range of different provisions e.g. health care professional letters, checklist for actions before prescribing or dispensing, patient information brochures or specific training programmes.
- Control of prescription size or validity. Prescription of a limited pack size will force the patient to see the physician at defined intervals giving the opportunity of pregnancy tests. Dispensing the medicinal product within a short period (e.g. 7 days) after prescription and in addition requesting the patient to return not used medicinal products.
- Informed consent about the possible risk associated with the medicinal product to ensure that the patient is appropriately informed.
- Patient registries to ensure that the recommended conditions of use are being applied.
- No samples to be offered.
- No repeated redemption of the prescription.
- No ordering by telephone or fax.

Another point is to assess the effectiveness of the applied risk minimisation activities. The activities must be modified and alternative methods used, if a particular risk minimisation strategy proves to be ineffective.

3.8.5 Post-marketing surveillance

Since little is known about the teratogenic potential of a medicinal product in humans before marketing, post-marketing pregnancy exposure registries are increasingly used to pro-actively monitor possible effects. Information is collected from women and physicians who contact the MAH to report drug exposure during pregnancy. For this reason a follow-up questionnaire may be sent to the physician or patient at pre-specified intervals to obtain outcome information if they give permission for later contact. The limitations are based on the voluntarily reporting system. Once a medicinal product has been on the market for several years, other epidemiological strategies, like case-control studies and secondary analyses of large population-based databases may be used to assess safety.

Reports are classified as prospective if the pregnant women are enrolled before the outcome of the pregnancy is known, as soon after exposure as possible and followed to the end of pregnancies. Cases where the condition of the fetus has already been assessed are considered as retrospective. If a live birth occurs, the pregnancy registry may follow the infant for a period of time. Retrospective cases are biased toward adverse outcomes since normal outcomes are rarely or not reported. Thus, the major strength of prospective registration is that patients are enrolled without prior knowledge of the possible adverse outcome, thus reducing the bias.

In the mid 1980ies, one of the first pregnancy registries, the Acyclovir Pregnancy Registry, was implemented by Burroughs Wellcome (now GlaxoSmithKline) (Andrews et al. 1988; Andrews et al. 1992). When other antiretroviral medicinal products were marketed, the registry expanded to a global registry (multi drugs and multi sponsors), called Antiretroviral Pregnancy Registry (Antiretroviral Pregnancy Registry Steering Committee 2007).

Pregnancy exposure registries are useful tools to signal possible problems which need further investigation, and to monitor risks suspected due to animal studies, pre-marketing clinical studies or post-marketing case reports. They are also useful to collect information on additional factors like dose and timing of exposure. However, the limitation of this approach is often that they are unlikely to enrol a sufficient number of exposed pregnancies to provide meaningful reassurance that a particular drug does not increase the risk of a specific defect.

Beside of company-run pregnancy registries different international registries offer public services to pregnant women and physicians. In Europe the following organisations may be contacted for questions concerning drug exposure during pregnancy:

- Organisation of Teratogen Information Services (OTIS) (http://www.teratology.org)
- European Network of Teratogen Services (http://entis-org.com)

  ENTIS was founded in Milan 1990. It coordinates the activities and studies of different information teratology services across Europe (Austria, Czech Republic, Finland, France, Germany, Greece, Italy, Lithuania, The Netherlands, Spain, Switzerland, Russia, United Kingdom) and other countries (Argentina, Brazil and Israel).
- European Surveillance of Congenital Anomalies (eurocat) (http://www.edurocat.ulster.ac.uk)

- International clearinghouse for Birth Defects Monitoring Systems (http://www.icbd.org)
- European collaboration of craniofacial anomalies (http://www.eurocran.org).

The advantage of international registries over national registries is an increased recruitment of patients and therefore a more robust sample size within a shorter time period. On the other hand there might be more heterogeneity in the study population.

4 Conclusion

In most cases pregnancies go well – the pregnant woman is healthy and the fetus develops normally - thus no intervention is necessary. However, sometimes a woman enters pregnancy with a preexisting medication, a health problem develops during pregnancy or the fetus has a condition requiring intervention. The number of those cases is on the increase since women are postponing childbirth until later in life, which increases the likelihood that they may suffer from medicinal problems prior to and during the pregnancy. In such cases the medicinal intervention to one may also affect the other.

Since the MAH almost never tests the medicinal product in pregnant women to determine its effect on the fetus, new medicinal products are generally not available for treatment during pregnancy. Typically descriptions in the SmPC and package leaflet of medicinal products contain statements like “safe use in pregnancy has not been established” with the warning that such medication ”should not be used in pregnant women unless the potential benefits justify the potential risks to the fetus.”

After the thalidomide disaster more than 40 years ago, the retreat to proven medicinal products for treatment and caution to apply new therapeutic options is understandable. Physicians, pharmaceutical industry, government agencies and pregnant women are long-term sensitized for possible teratogen effects and future effects on development of the fetus after medicinal product exposure. Case reports on malformations are available for numerous medicinal products, but studies with statistical validity are often missing.

During the clinical development program of most medicinal products, pregnant women are actively excluded from trials, and if pregnancy occurs during a trial, the usual procedure is to discontinue treatment and drop the patient from the study. Including pregnant women in clinical trials, particularly evaluating safety and efficacy of medicinal products is a complex issue. The profound problems are the physiological changes during the different phases of pregnancy, and the fetoplacental unit which is actively involved in transport and metabolism. Other challenges are patient recruitment, the need to modify design protocols differing from those developed for the nonpregnant women, and the ethical situation since pregnant women are classified as a vulnerable population requiring special protection. Further aspects are that conducting clinical trials in the population of pregnant women may have the risk of a bad reputation, a probably perceived poor market and less utilization of the medicinal product compared with the general population, causing the pharmaceutical industry to prefer a strict labelling.

The need to include pregnant women into clinical trial programs is given if this is the only source of a promising experimental therapy for a life-threatening condition. This is especially important if the medicinal nihilism may lead to a dramatic deterioration of the disease, causing a higher risk for the development of the embryo and/or the fetus. The best example

is the courageous study protocol 076 conducted by “The Pediatric AIDS Clinical Trial Group” which demonstrated that zidovudine, administered to the mother after the first trimester of pregnancy as well as during labor and delivery, and to the newborn for the first six weeks of life reduces the risk of the maternal-infant transmission of HIV-1 by approximately two thirds (Connor et al. 1994). The striking data at the first interim analysis of efficacy induced the “Data and Safety Monitoring Board” to discontinue the clinical study for ethical reasons and to offer all participating patients zidovudine (Connor et al. 1994). Currently this therapeutic regimen is the basis for the “gold standard” to reduce the risk of HIV-1 transmission from mother to the newborn.

Unquestionably, the association of maternal and embryonal/fetal condition is very close. Recently published epidemiologic studies suggest that influences linked to *in utero* development and placental growth have an important effect on the incidence of certain adult diseases, such as stroke and coronary heart disease (Barker 1998). In studies exploring the mechanisms underlying these associations, the correlation between coronary heart disease and birthweight were found to be paralleled by similar trends in two of its major risk factors – hypertension and Type II diabetes mellitus (Barker et al 1989). Thus *in utero* programming has not only profound effects on the developing fetus but has also an impact on the overall health in adulthood.

It is amazing that world-wide governments do not make more efforts to close the gap of missing human data by pro-active monitoring each individual outcome of pregnancy after medicinal product exposure (intended or unintended) via pregnancy exposure registries, and to establish corresponding data bases. Since there is no systematic post-marketing surveillance of medicinal product exposed pregnancies after approval of a medicinal product, the observations result in an over-representation of recorded adverse outcomes, while little information is available on the number of pregnancies with normal outcome (Sannerstedt et al. 1996). Case reports are mostly retrospective, due to their potential for bias, they should not be used alone to identify increased prevalence of adverse events. The initial suggestions that benzodiazepines, spermicides, and Bendectin were teratogenic were based on retrospective case-control studies subsequently proven false by other, larger studies (Briggs et al. 2005; Koren 1998).

For an extended period of time, and due to the lack of sufficient and reliable human data the risk assessment is based on preclinical studies and isolated case reports for the majority of products, whether newly marketed or commercially available for a longer period of time. However, the helpfulness of animal studies are limited since known teratogenic substances in humans are also harmful in suitable preclinical tests, but in contrary frequently observed toxic effects in the treated animals are not always hazardous to humans. Newer medicinal products may have less adverse effects or may be more effective for the adult, but their safety for the fetus may be not or less known, resulting in a persistent warning for use during pregnancy.

Unfortunately, an analysis of the risk classification systems - and consequently the labelling - of different countries revealed a range of discrepancies based on different criteria for assignment, conflicting interpretation of the original data sources with the result that the same drug was classified in different categories (Addis et al. 2000; Sannerstedt et al. 1996). Further, the classification schemes seldom take into account the different stages of pregnancy and critical periods of fetal susceptibility. In most publications the first trimester of pregnancy is considered the most critical period for major congenital malformations. Bánhidy

and collegues (2005) stated that this concept is outdated, since the critical period of some congenital malformations exceeds the end of third month, e.g. the critical period of posterior cleft palade and hypospadias covers the 12^{th}-14^{th} and 14^{th}-16^{th} weeks of gestation, while the critical period of undescended testis and patent ductus arteriosus is 7-9 months and 9-10 months, respectively. Thus the optimal approach is to consider the specific critical periods of each congenital malformation separately. Many medications might not be used during a certain period of pregnancy, but might be safe in an earlier or later phase.

In addition, the systems do not address the indication for which the medicinal product is used, as well as the route of administration. Thus the criteria to assess and label a medicinal product for treatment of headache are the same as for treatment of cancer or seizure. According to Wilson (1977) the extent of an embryonal/fetal injury caused by exogenous agents is proportional to the dose. After exceeding a certain threshold, which is individual for each drug substance, a toxic range is reached followed by embryonal/fetal or maternal toxic effects, respectively. This is important for the route of administration, since e.g. topically used agents rarely reach the same blood concentrations as systemically applied medicinal products do. Therefore it is necessary to evaluate the teratogenic potential of a medicinal product according to it's route of administration. For example, corticosteroids can be applied orally, topically (skin, vaginal, eye and ear), parenteral or may be inhaled as aerosol, thus these different routes of administration can cause different adverse effects for the same active substance (Bánhidy 2005). Currently, missing data e.g. for topical use are replaced in SmPC and package leaflet by data collected during systemic application and the additional hint, that "the benefit must be weighed against the potential risk". The present trend is to report in detail the available information and let the physician and patient decide how to interpret this information. This philosophy leads to problems since it supposes that the average doctor is able to interpret the data.

Another possibility to determine agents posing potential risks of adverse effects after exposure to the fetus is to identify genetic differences in maternal or fetal genes that may influence the susceptibility towards medicinal products. This is very probably since "high risk-teratogens" like thalidomide or isotretinoin, which cause a variety of malformations in approximately 25-30% of cases, do not affect all exposed fetuses, even if given during the critical period. Many researches believe that this differential effect is at least in part due to genetically determined host factors (Depond et al. 2006; Leeder and Mitchel 2007; Lidral and Murray 2004). Until now successful approaches to identify genetic polymorphisms responsible for medicinal product induced birth defects are limited. Genetic approaches like microarray technology, single nucleotide polymorphism genotyping, proteomics and metabolomics data sets of expressed genes during critical periods of development could help to identify genes causing or contributing to congenital malformations (Lidral and Murray 2004, Park et al. 2006). At present time, this promising approach is limited since much data will need to be generated, shared, and analyzed before the association of genetic variation and the individual benefits and risk of medicinal products can be establised.

The decision whether to treat or not to treat a pregnant woman with medicinal product(s) is an issue of risk management. In situations in which a "normal" patient is administered the necessary medicinal product without any doubts, pregnant women or potentially pregnant women may be treated after thorough consideration of all pros and cons. The cons are mainly due to potential teratogenic effects on the fetus after medicinal product exposure. On the other hand reluctant therapeutically intervention may also have serious consequences for both the mother and her fetus. Hyperthermia, a symptom often associated with other

diseases, may induce hyperthermic embryopathy if not treated by appropriate methods (Bánhidy 2005).

Unless the physician selects an established “old” medicinal product, the SmPC contains the conclusion that “no risk exists for the fetus” or “the medicinal product is contraindicated during pregnancy”, respectively, the physician has to outweigh the risks versus the benefits - pursuant to the individual situation.

Since mostly the labelling of medicinal products contains statements like “safe use in pregnancy has not been established”, the physician has to spend the time searching for appropriate scientific literature. It is a matter of question whether the animal data, provided in section 5.3 Preclinical safety data (SmPC) are helpful for risk assessment. It can’t be quantified, but probably every decision is influenced by possible law suits, forgetting that the outcome of every pregnancy ending with a malformed baby is about 3%, even if no medicinal product was administered during pregnancy. But what to do if no appropriate medicinal product is available? Often the decision for a medicinal product will end up in an off label use, since only a minority of medicinal products is indicated for use during pregnancy, or the medicinal product should not be given for safety reasons, respectively. According to German law, the use of a medicinal product is not illegal despite a missing indication for use in pregnancy, if it is shown that the medicinal product is effective and safe and no other alternative option is available (Schaefer and Weber-Schöndorfer 2005). The safety of the medicinal product is a relative definition, forcing the physician to decide on the benefit/risk assessment whether a medicinal product intervention is necessary, and if yes which medicinal product should be administered. Based on the “Aciclovir-Judgement” of the *Oberlandesgericht Köln* (30.5.1990 – 27 U 169/87), in certain situations like a severe disease and the need for therapy, even an obligation for application may derive.

Every physician should keep in mind that there is also the approach to clarify the best option for treatment by contacting one of the information centres for reproductive toxicology (e.g. ENTIS) offering public services to pregnant women and their physicians. The problem is that not all physicians and women know about this chance to get help free of charge.

In order to provide more security for all persons concerned, mainly three activities should be brought into focus:

- Governmental-run pregnancy exposure registries with sufficient staff and financial facilities to keep a closer contact to physicians and exposed women, since pregnancy exposure registries offer the unique opportunity to collect information on all pregnancy exposures early in a product’s lifecycle.
- More clinical trials in pregnant women might be a chance to get more reliable information concerning the risks and benefits in humans.
- Improvement of labelling with more narrative and informative texts, taking into account individual facts, e.g. indication, the route of administration, pregnancy status, magnitude of exposure (incidental exposure versus chronic exposure), and timing of exposure.

At last it should be mentioned that the awareness of potential risks during pregnancy should also include a dangerous lifestyle e.g. stress, environmental pollution, consuming alcohol, and smoking tobacco. It is estimated that every year about 500 to 800 children are born with fetal alcoholic syndrome and about 4.000 to 5.000 children with “weaker” adverse effects after exposure to alcohol during pregnancy (Schaefer and Weber-Schöndorfer 2005). In

addition, nicotine abuse increases the risk for terminal transverse type of limb deficiencies and Poland sequence (Czeizel et al. 1994; Martinez-Friaz et al. 1999).

5 Summary

Women who discover they are pregnant after exposure to a medicinal product and pregnant women who require continued treatment during pregnancy are told to balance the benefits and risks of exposure to justify continuation of treatment, discontinuation of treatment or even terminate the pregnancy. The profound effects that drugs and other chemicals can have on the fetus were brought into clear focus with the thalidomide disaster in the early 60ies (Dally 1998). Many babies were born with severe deformities of arms, legs and other malformations.

This finding brought attention to the possibility that other medicinal products could have similar effects on the fetus. It has been shown that any medicinal product or chemical substance administered to the mother is able to cross the placenta to some extent, unless it is destroyed or altered during passage, or its molecular size and low solubility limit transplacental transfer (Syme et al. 2004).

When a new medicinal product is approved the risk assessment is based on animals reproductive toxicology studies and clinical studies done on male and nonpregnant women leading to a lack of scientific knowledge of the clinical pharmacology, pharmacokinetics and pharmacodynamics of the medications administered during pregnancy. Unless a product is intended specifically for use during pregnancy, pregnant women are actively excluded from clinical trials. If pregnancy occurs during a trial, the usual procedure is to discontinue treatment and drop the patient from the study.

Missing or insufficient human data are reflected in a restricted labelling of new medicinal products with contraindications, special warnings and strictly benefit/risk assessment causing physicians to avoid therapeutic regimen. Especially for expecting mothers with chronic diseases as bronchial asthma, psychiatric disorders, epilepsy or hypertension, therapeutic nihilism may lead to a dramatic deterioration of the disease, and this may also induce a higher risk for the fetal development. On the other hand numerous abortions without profound indications are carried out due to insufficient information of patients and medical staff concerning the real risk of a medicinal product used during early pregnancy.

To determine the relationship between exposure to a medicinal product and fetal outcome the collection of post-authorisation data is needed and the responsible marketing authorisation holder is obliged to introduce a pro-active monitoring. The limitation of this approach is that first of all the physician or the pregnant woman must report any medicinal product exposure. This takes place more or less only after an adverse outcome of pregnancy occured. If the medicinal product in question has a strong teratogenic potential or causes rare malformation then a reasonable suspicion arises early. The more difficult scenario is given if the medicinal product acts as “moderate or low-risk teratogen”, then a broad range of data is necessary to determine whether the medicinal product has an adverse effect on the embryo/fetus. Since there is no systematic post-marketing surveillance of all exposed pregnancies after approval of a medicinal product, the observations result in an over-representation of recorded adverse outcomes.

The decision whether to treat or not to treat a pregnant woman with medicinal product(s) is an issue of risk management. In situations in which a “normal” patient is administered the necessary medicinal product without any doubts, pregnant women or potentially pregnant women may be treated after thorough consideration of all pros and cons. The cons are

mainly due to potential teratogenic effects on the fetus after medicinal product exposure. On the other hand reluctant therapeutically intervention may also have serious consequences for both - mother and fetus.

6 References

ADEC. Australian Drug Evaluation Committee. Medicines in Pregnancy. An Australian Categorization of Risk, 1992.

Alvan G, Kihlström I, Prame B, Ridley E, Sannerstedt R. Classification of drugs for teratogenic risk. Eur J Clin Pharmacol 1995;48:177-178.

American Academy of Pediatrics. Use of psychoactive medication during pregnancy and possible effects on the fetus and newborn. Pediatrics 2000;105:880.

Andrews EB, Tilson HH, Hurn BA, Cordero JF. "Aciclovir in Pregnancy Registry. An observed epidemiologic approach." Am J Med 1988;85;123-8.

Andrews EB, Yancascas BC, Cordero JF, Schoeffler K, Hampp S. "Aciclovir in pregnancy: six years' experience." The Aciclovir in Pregnancy Registry Advisory Committee. Obstet Gynecol 1992;79:7-13.

Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry Advisory International Interim Report for 1 January 1989 through 31July 2007. Wilmington, NC: Registry Coordinating Center; 2007. *Available from www.apregistry.com*

Audus KL. Controlling drug delivery across the placenta. Eur J Pharm Sci 1999;8:161-165.

Bánhidy F, Lowry RB, Czeizel AE. Risk and benefit fo drug use during pregnancy. Int. J. med. Sci. 2005;2(3):100-106.

Barker DJP. *In utero* programming of chronic disease. Clinical Science 1998;95:115-128.

Barker DJP, Osmond C, Golding J, Kuh D, Wadsworth MEJ. Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. Br. Med. J. 1989;298, 564-567.

Barr M and Burti AR. Warfarin-associated embryopathy in a 17-week-old abortus. Teratology 1976;14(2):129-34.

Barret C, Richens A. Epilepsy and pregnancy: Report of an Epilepsy Research Foundation Workshop. Epilepsy Res 2003;52:147.

Benet LZ, Massoud N, Bambertoglio JG. Pharmacokinetic basis for drug treatment. New York: Raven Press, 1984.

Bernstein A. Formed by thalidomide: mass torts as a false cure for toxic exposure. Columbia Law Rev 1997;97:2153-76.

Bracken MB. Oral contraception and congenital malformations in off-spring: a review and meta-analysis of the prospective studies. Obstet Gynecol 1990;76:552-7.

Briggs GG, Freeman RK, Yaffe SJ. Drugs in pregnancy and lactation. 4th ed. Baltimore: Williams & Wilkins, 1994.

Briggs GG, Freeman RK, Yaffe SJ. Drugs in Pregnancy and lactation 7th ed. Baltimore: Williams & Wilkins, 2005.

Brushwood DB. Two legal issues: Expert witnesses and Bendectin case. Drug Intell Clin Pharm 1983;17:848-849.

Carney EW, Scalli AR, Watson RE, DeSesso JM. Mechanisms regulating toxicant disposition to the embryo during early pregnancy: An interspecies comparison. Birth Defects Research (Part C) 2004;72:345-360.

Center for Drug Evaluation and Research. Guideline for the format and content of the clinical and statistical sections of new drug applications. Washington, DC.: Food and Drug Administration.

Christie GA. Thalidomide and congenital abnormalities. Lancet 1962;2:249-249.

Collaborative Group on Drug Use in Pregnancy. An International Survey on Drug Utilization During Pregnancy. International Journal of Risk and Safety in Medicine, 1991;1:1.

Committee on Drugs. American Academy of Pediatrics: the transfer of drugs and other chemicals into human milk. Pediatrics 1994;93:858-68.

Connor EM, Sperling RS, Gelber R, et al. for The Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. Reduction of maternal-infant transmission of Human Immundeficiency Virus Type 1 with Zidovudine treatment. N Engl J Med 1994;331:1173-80.

Czeizel AE, Kodaj I, Lenz W. Smoking during pregnancy and congenital limb deficiency. Brit Med J 1994;308:1473-1476.

CPMP/ICH/386/95 (ICH S5A) and CPMP/ICH/136/95(ICH S5B); ICH S5(R2): Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility.

CPMP/ICH/286/95 (ICH M3[M]): Note for Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals.

CHMP/ICH/5716/03 (ICH E2E) Pharmacovigilance Planning (Pvp): Note for Guidance on Planning Pharmacovigilance Activities Planning.

Dally A. Thalidomide: Was the tragedy preventable? Lancet 1998;35:1197-9.

Depond C, Shorvon SD. Genetic association studies in epilepsy pharmacogenomics: lessons learnt and potential applications. Pharmacogenomics 2006 Juli;7(5):731-45.

Dickson JH. Congenital deformities associated with Bendectin. Can Med Assoc J 1977;117:721.

Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to Medicinal Products for Human Use, as amended by Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003, Directive 2004/24/EC of the European Parliament and the Council of 31 March 2004, Directive 2004/27/EC of the European Parliament and the Council of 31 March 2004, and Directive 2003/63/EC of 25 June 2003.

Discussion Paper on Contraindication in Pregnancy Concerning Sections 4.3, 4.6 and 5.3 of the Summary of Product Characteristics (CPMP/3833/03).

Doering PL, Boothby LA, Cheok M. Review of pregnancy labeling of prescription drugs: is the current system adequate to inform of risks? Am J Obstet Gynecol 2002;187:333-339.

Donnai D, Harris U. Unusual fetal malformations after antiemetics in pregnancy. BMJ 1978;1:691-2.

Draft Guideline on Non-Clinical Documentation for Herbal Medicinal Products in Applications for Marketing Authorisation (Bibliographical and mixed applications) and in Applications for Simplified Registration (EMEA/HMPC/32116/05).

Durk HA. Maintenance therapy for multiple myeloma with particular emphasis on thalidomide. Onkologie. 2006 Dec;29(12):582-90. Epub 2006 Dec 11.

Einarson TR, Koren G, Mattie D, Schechter-Tsafiri O. Maternal spermicide use and adverse reproductive outcome: a meta-analysis. Am J Obstet Gynecol 1990;4:39-42.

Einarson TR, Leeder JS, Koren G. A method for meta-analysis of epidemiological studies. Drug Intell Clin Pharm 1988;22:813-24.

Enns GM, Roeder E, Chan RT, Ali-Khan Catts Z, Cox VA, Golabi M. Apparent cyclophosphamide (cytoxan) embryopathy: a distinct phenotype? Am J Med Genet 1999;86:237-41.

Eriksson T, Björkmann S, Roth B, Höglund P. Intravenous formulations of the enantiomers of thalidomide: pharmacokinetic and initial pharmacodynamic characterization in man. J Pharm Pharmacol 2000 Jul;52(7):807-17.

Eriksson T, Björkmann S, Roth B, Fyge A, Höglund P. Stereospecific determination, chiral inversion in vitro and pharmacokinetics in humans of the enantiomers of thalidomide. Chirality 1995;7(1):44-52.

Evans WE, Schentag JJ, Jusko WJ (1986). Applied pharmacokinetics: principles of therapeutic drug monitoring (Applied Pharmacokinetics) (Paperback).

Fantel AG, Shepard TH, Newell-Morris LL, Moffett BC. Teratogenic effects of retinoid acid in pigtail monkeys (Macaca nemestrina). I. General features. Teratology 1977;15:65-71.

FASS. Classification of medicinal products for use during pregnancy and lactation. The Swedish system. Stockholm: LINFO, Drug Information Ltd., 1993.

FDA: Food and Drug Administration Center for Evaluation and Research Pregnancy Labeling Subcommittee of the Advisory Committee for Reproductive Health Drugs [cited 2001 Mar 26]. Available from: URL: http://www.fda.gov/ohrms/dockets/ac/00/transcripts/3601tl.rtf

Fredericksen MC. Physiologic changes in pregnancy: Effect on drug disposition. FDA Center for Drug Evaluation and Research, 2000.

Fromm MF. Importance of P-glycoprotein at blood-tissue barriers. Trends Pharmacol Sci 2004;25:423-429.

Ganapathy V, Prasad PD, Ganapathy ME, Leibach FH. Placental transporters relevant to drug distribution across the maternal-fetal interface. J Pharmacol Exp Ther 2000;294:413-420.

Ganapathy V, Prasad PD. Role of transporters in placental transfer of drugs. Toxicol Appl Pharmacol 2005;207(Suppl 1):381-387.

General Accounting Office. Women's health: FDA needs to ensure more study of gender differences in prescription drug testing. Washington, D.C.: Government Printing Office, 1992. (Publication no. GAO/HRD-9317.)

Guideline on the Exposure to Medicinal Products: Need for Post-Authorisation Data (EMEA/CHMP/313666/2005).

Guideline on Non-Clinical Documentation for Mixed Marketing Authorisation Applications (CPMP/SWP/799/95).

Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: From Data to Labelling (EMEA/CHMP/203927/2005).

Guideline on Risk Management Systems for Medicinal Products for Human Use (EMEA/CHMP/96268/2005).

Guideline on Summary of Product Characteristics is included in The Rules Governing Medicinal Products in the European Union Volume 2C Notice to Applicants.

Holmes LB. Teratogen update: Bendectin. Teratology 1983;27:277-281.

Jick H, Walker AM, Rothman KJ et al. Vaginal spermicides and congenital disorders. JAMA 1981;245:1329-32.

Juchau MR. Bioactivation in chemical teratogenesis. Ann Rev Pharmacol Toxicol 1989;29:165-87.

Kalter H. Teratology in the 20th century. Environmental causes of congenital malformations in humans and how they were established. Neurotox Teratol 2003;25:131-282.

Kamm JJ. Toxicology, carcinogenicity, and teratogenicity of some orally administered retinoids. J Am Acad Dermatol 1982;6652-9.

Khouri MJ, Beaty TH, Hwang SJ. Detection of genotype-environment interaction in case-control studies of birth defects: How big a sample size? Teratology 1995;51:336-43.

Koren G, Pastuszak A, Shinya S. Drugs in pregnancy. N Engl J Med 1998;338:1128-37.

Lammer EJ, Chen DT, Hoar RM, Agnish ND, Benke PJ, Braun JT, Curry CJ, Fernhoff PM, Grix AW, Lott IT. Retionic acid embryopathy. N Engl J Med 1985;Oct 3;313(14):837-41.

Leeder JS and Mitchell AA. Application of pharmacogenomic strategies to the study of drug-induced birth defects. Clinical Pharmacology & Therapeutics 2007;81(4):595-599.

Lenz W. Kindliche Fehlbildungen nach Medikament während der Gravidität? Dtsch Med Wochenschr 1961;86:2555-6.

Lenz W, Knapp K. Die Thalidomid-Embryopathie. Dtsch Med Wochenschr 1996;87:1232-42.

Lidral AC and Murray JC. Genetic approaches to identify disease genes for birth defects with cleft lip/palate as a model. Birth defects Res. A Clin Mol. Teratol 2004;70:893-901.

Loebstein R, Lalkin A, Koren G. Pharmacokinetic changes during pregnancy and their clinical relvance. Clin Pharmacokinet 1997;33:328-43.

Magee LA, Elran E, Bull SB, Logan AG, Koren G. Risks and benefit of b-receptor blockers for pregnancy hypertension: Overview of the randomized trials. Eur J Obstet Gynecol Reprod Biol 2000;88:15.

Mann MW, Pons G. Various pharmacogentic aspects of antiepileptic drug therapy: a review. CNS Drug, 2007;21(2):143-64.

Martinez-Friaz ML, Czeizel AE, Rodriquez-Pinilla E, Bermejo E. Smoking during pregnancy and Poland sequence: Results of a population based registry and a case-control registry. Teratology 1999;59:35-38.

McKeigue PM, Lamm SH, Linn S, Kutcher JS. Bendectin and birth defects. I. A meta-analysis of the epidemiologic studies. Teratology 1994;50:27-37.

Miller MT, Stromland K. Teratogen update: Thalidomide: A review, with the focus on ocular findings and new potential uses. Teratology 1999;60:306-321.

Mölsä M, Heikkinen T, Hakkola J, Hakala K, Wallerman O, Wadelius M, Wadelius C, Laine K. Functional role of P-glycoprotein in the human blood-placental barrier. Clin Pharmacol Ther 2005;78:123-131.

Note for Guidance on Reproductive Toxicology: Detection to Reproduction of Toxicity to Reproduction for Medicinal Products (CPMP/ICH/386/95).

Note for Guidance on Specific Regulatory Genotoxicity Tests for Pharmaceuticals (CPMP/ICH/141/95).

Note for Guidance on Gentoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals (CPMP/ICH/174/95).

Nora JJ, Nora AH, Blu J, et al. Exogenous progesterone and estrogen implicated in birth defects. JAMA 1978;240:837-43.

Notice to Applicants Volume 9A of The Rules Governing Medicinal Products in the European Union.

Oberlandesgericht Köln – Urteil vom 30.5.1990 – 27 U 169/87. Grober Behandlungsfehler eines Arztes wegen Nichteinsatz eines für eine bestimmte Indikation noch nicht zugelassenen Arzneimittels.

Ornstein M, Einarson A, Koren G. Bendectin/Diclectin for morning sickness: a Canadian follow-up of an American tragedy. Reprod Toxicol 1995;9:1-6.

Pacifici GM, Nottoli R. Placental transfer of drugs administered to the mother. Clin Pharmacokinet 1995;28:235-269.

Park JW, Cai J, McIntosh I, Jabs EW, Fallin MD, Ingersoll R, Hetmanski JB, Vekemans M, Attie-Bitach T, Lovett M, Scott AF, Beaty TH. High throughput and expression analysis of candidate genes for nonsyndromic oral clefts. J. Med. Genet. 2006;43:598-608.

Pastuszak AL, Koren G, Rieder MJ. Use of the Retionoid Prevention Program in Canada: patterns of contraception use in women treated with isotretionoin and etretinate. Reprod Toxicol 1994;8:63-8.

Paulus WE. Pharmacotherapy in pregnancy. Ther Umsch 1999;56(10):607-10.

Phanuphak P. Ethical issues in studies in Thailand of the vertical transmission of HIV. N Engl J Med. 1998 Mar 19;338(12):834-5.

Pschyrembel Klinisches Wörterbuch, Walter de Gruyter Verlag, Berlin.

Raman-Wilms L, Tseng AL, Wighardt S, Einarson TR, Koren G. Fetal genital effects of first-trimester sex hormone exposure: a meta-analysis. Obstet Gynecol 1995;85:141-9.

Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.

Rosa FW. Teratogenicity of isotretinoin. Lancet 1983;2:513.

Rosenberg L, Mitchell AA, Parsell JL, Pashayan H, Luvik C, Shapiro S. Lack of relation of oral clefts to diazepam use during pregnancy. N Engl J Med 1983;309:1282-5.

Rote Liste, Service GmbH, Frankfurt am Main

Sales AM, de Matos HJ, Nery JA, Duppre NC, Sampaio EP, Sarno EN. Double-blind trial of the efficacy of pentoxifylline vs thalidomide for the treatment of type II reaction in leprosy. Braz J Med Biol Res. 2007 Feb;40(2):243-8.

Sannersedt R, Lundborg P, Danielsson BR, Kihlstrom I, Alvan G, Prame R et al. Drug during pregnancy: an issue of risk classification and information to precribers. Drug Saf 1996;14;69-77.

Saxen I. Association between oral clefts and drugs taken during pregnancy. Int J Epidemiol 1975;4:37-44.

Schaefer C, Spielmann H, Vetter K. Arzneiverordnung in der Schwangerschaft und Stillzeit. 7. Auflage, München: Urban & Fischer Verlag.

Schaefer C and Weber-Schöndorfer C. Medikamentöse Therapie in der Schwangerschaft. Deutsches Ärzteblatt; Jg. 102; Heft 37; 16. September 2005.

Schardein JL. Congenital abnormalities and hormones during pregnancy: a clinical review. Teratology 1980;22:251-70.

Schardein JL, Schwetz BA, Kenel MF. Species sensitivities and predicition of teratogenic potential. Environ Health Perspect 1985;61:55-67.

Shalita AR, Cunningham WJ, Leyden JJ, Pochi PE, Strauss JS. Isotretinoin treatment of acne and related disorders: an update. J Am Acad Dermatol 1983;9:629-38.

Shiono PH, Mills JL. Oral clefts and diazepam use during pregnancy N Engl J Med 1984;311:919-20.

Slone D, Siskind V, Heinonen OP, Monson RR, Kaufman DW, Shapiro S. Aspirin and congenital malformations. Lancet 1976;1:1373-5.

Syme MR, Paxton JW, Keelan JA. Drug transfer and metabolism by the human placenta. Clin Pharmacokinet 2004;43:487-514.

Trent DS and Fillimore BJ. Hypothesis: Thalidomide embryopathy – proposed mechanism of action. Teratology 2000;61:189-195.

Uhl K, Kennedy DL, Kweder SL. Risk management strategies in the Physicians' Desk Reference product labels for pregnancy category X drugs. Drug Saf 2002;25:885-892.

Villahermosa LG, Fajardo TT Jr, Abalos RM, Balagon MV, Tan EV, Cellona RV, Palmer JP, Wittes J, Thomas SD, Kook KA, Walsh GP, Walsh DS. A randomized, double-blind, double-dummy, controlled dose comparison of thalidomide for treatment of erythema nodosum leprosum. Am J Trop Med Hyg. 2005 May;72(5):518-26.

Walker BE. Induction of cleft palade in rats with anti-inflammatory drugs. Teratology 1971;4:39-42.

Ward RM. Difficulties in the study of adverse fetal and neonatal effects of drug therapy during pregnancy. Seminars in Perinatolgy 2001;25, No3(June):191-195.

Werler MM, Mitchell AA, Shapiro S. The relation of aspirin use during the first trimester of pregnancy to congenital cardiac defects. New Engl J Med 1989;321:1639-42.

Wilson JD. Embryotoxicity of drugs to man. In: Wilson JD, Frazer FC, eds. Handbook of Teratology. New Xork, London: Plenum Press, 1977:309-55.

Wikipedia Encyclopedia

Wilson JG, Ritter EJ, Scott WJ, Fradkin R. Comparative distribution and embryotoxicity of acetylsalicylic acid in pregnant rats and rhesus monkeys. Toxicol Appl Pharmacol 1977;41:67-78.

Zustovich F, Cartei G, Ceravolo R, Zovato S, Della Puppa A, Pastorelli D, Mattiazzi M, Bertorelle R, Gardiman MP. A phase I study of cisplatin, temozolomide and thalidomide in patients with malignant brain tumors. Anticancer Res. 2007 Mar-Apr;27(2):1019-24.

7 Annex – Definitions

Anotia: is the congenital absence of one or both external ears.

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

Congenital anomaly: 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, developmental delay, 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.

Dandy-Walker syndrome: congenital brain malformation involving the fourth ventricle and cerebellum.

Ductus arteriosus: is a key arterial shunt (ductus) in fetal life. Before birth, blood pumped from the heart through the pulmonary artery toward the lungs is shunted into the aorta. The ductus arteriosus usually closes at or shortly after birth, permitting blood from that moment on to course from the heart directly to the lungs.

Ebstein's anomaly: congenital heart defect in which the opening of the tricuspid valve is displaced towards the apex of the right ventricle of the heart.

Ectopic pregnancy: extrauterine pregnancy, early fetal death most often in the Fallopian tube.

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).

Epididymis: part of the human reproductive system and is present in all male mammals. It is a narrow, tightly-coiled tube connecting the efferent ducts from the rear of each testicle to its vas deferens.

Fertility (male and female): the actual reproductive performance of an individual, a couple, a group, or a population, and thus the failure to reproduce defines infertility. Clinical attention is generally restricted to couples who have experienced unprotected intercourse that does not result in a conception for at least one year.

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.

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 10). Early fetal death (before 22 completed weeks of

gestation) comprises ectopic pregnancy and miscarriage and late fetal death (after 22 completed weeks of gestation) is known as stillbirth.

Genetic Polymorphism: is a DNA sequence variation occurring when a single nucleotide - A, T, C, or G - in the genome (or other shared sequence) differs between members of a species (or between paired chromosomes in an individual). For example, two sequenced DNA fragments from different individuals, AAGC**C**TA to AAGC**T**TA, contain a difference in a single nucleotide.

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).

Hypospadias: is a birth defect of the urethra in the male that involves an abnormally placed urethral meatus (opening). Instead of opening at the tip of the glans of the penis, a hypospadic urethra opens anywhere along a line (the *urethral groove*) running from the tip along the underside (ventral aspect) of the shaft to the junction of the penis and scrotum or perineum.

Icterus neonatorum: yellowish appearance in newborn infants; usually subsides spontaneously.

***In utero* programming**: describes the process whereby a stimulus of insult at a critical period of development has lasting or lifelong effects.

Incidence: 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.

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.

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

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).

Low birth weight: less than 2.500 gram (up to and including 2.499 g) of body weight of the newborn at birth.

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 to 4 % in most series published.

Meconium ileus: Obstruction of the intestine (ileus) due to overly thick meconium, the dark sticky stuff that is normally present in the intestine at birth and, after trypsin and other enzymes from the pancreas have acted on it, is normally passed in the feces after birth. Meconium ileus results from a deficiency of trypsin and other digestive enzymes from the pancreas.

Metabonomics: The study of metabolic responses to drugs, environmental changes and diseases. Metabonomics is an extension of genomics (concerned with DNA) and proteomics (concerned with proteins). Following on the heels of genomics and proteomics,

metabonomics may lead to more efficient drug discovery and individualized patient treatment with drugs, among other things.

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

Miscarriage: spontaneous abortion, molar pregnancy.

Mobius syndrome: is caused by abnormal development of the cranial nerves. Common Symptoms: abnormal facial features, droopy eyelid(s), abnormal finger(s), delayed development.

Neonatal withdrawal syndrome: commonly occurs in infants exposed during the third trimester to medicinal products known to cause addiction.

Phocomelia: a congenital deformity resulting from prenatal interference with the development of the fetal limbs, characterized especially by short stubby hands or feet attached close to the body.

Poland sequence: a unique pattern of one-sided malformations characterized by a defect of the chest (pectoralis) muscle on one side of the body and webbing of the fingers (cutaneous syndactyly) of the ipsilateral hand (the hand on the same side).

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

Preembryo: the first stage of prenatal (see also 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.

Pregnancy outcome: the end products of pregnancy which include three main categories: fetal death, termination of pregnancy and live birth.

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

Proteomics: describes the technology that is able to identify proteins expressed from a genome at a certain time point under strictly defined conditions, the proteome.

Reproductive toxicity studies: animal studies to reveal any effects on the female or male reproductive organs or the related endocrine systems.

Single Nucleotide Polymorphism: is a DNA sequence variation occurring when a single nucleotide - A, T, C, or G - in the genome (or other shared sequence) differs between members of a species (or between paired chromosomes in an individual).

Teratogens: environmental factors which can cause congenital abnormalities.

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

Termination of pregnancy (induced abortion, elective abortion): artificial interruption of pregnancy.

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

München, den