Module 11 – Special Scenarios in Pharmacovigilance

Contents

1. Introduction

This chapter includes some topics that require special attention, more than routine case processing. Special topics included here are

- Conducting Pharmacovigilance in Paediatrics Population
- Monitoring the Exposure to Medicinal products in Pregnancy
- Processing the Reports of Medication Error

Knowledge about these special scenarios is critical when it comes to processing individual cases. It further extends the need when performing aggregate reporting and signal detection activities. There are sections within the aggregate reports which are dedicated to these special scenarios and are monitored on an ongoing basis.

Unless the processing of the individual cases is appropriate the activities related to safety surveillance would not yield fruit. As a result, regulatory authorities have shared there thinking on how cases from these special scenarios need to be handled.

Some of the elements of these special topics interlace with other statutory documents or activities; e.g. Paediatric case processing has a cross reference to the Paediatric Investigation Plan (PIP).

Moreover – While the data handling conventions may differ from one organization to another but would and should be defined in the company Standard Operating Procedures (SOPs). Therefore, often, a holistic approach to understand an organization's approach to these special situations is important.

2. Conducting Pharmacovigilance in Paediatric Population

Paediatric population is considered a special population and includes person aged between 0 and 18 years. US FDA defines children as, “for drugs, a child is defined as a person up to 17 years of age for devices, 21 years of age is the upper limit.”

Due to the dynamic process of maturation, there are developmental charges in physiology and consequently in pharmacology, this affecting the efficacy, toxicity and dosing regimens of medicines used in children. Therefore, children cannot be considered as small adults.

Drug metabolism in children may be different from adults Childhood diseases and disorders may also be qualitatively and quantitatively different from their adult equivalents. Due to the ongoing maturation in this age group, Growth and development disorders, as well as delayed adverse drug reactions may be observed in theses age groups which are usually not seen in adults. Long term follow-up data is desirable to detect such effects. Therefore, during clinical development, special studies should be conducted in paediatric population and follow-up should be planned accordingly.

For most of the medicinal products, data is limited at the time of initial authorization. Even when paediatric clinical trials have been conducted, clinical data may not be sufficient if clinical trials have not been conducted in all paediatric age groups. Thus, it is very important to appropriately monitor safety of the medicinal products for paediatric use after marketing.

Paediatric population is further classified as preterm and term new-born infants, infants and toddlers, children and adolescents and these groups represent a spectrum of different physiologies. Safety data from adult population cannot be extrapolated in paediatric population and only limited data is generated during the clinical development.

Sample size in phase I and II trials are usually small and does not include paediatric population for ethical reasons. In phase III trials, sample size is nearly always based on the end-points for efficacy. Thus, small sample size limits the ability to observe rare and very rare adverse reactions.

Serious adverse reactions, where there is a lag period between the drug administration and onset of the adverse reactions are generally not observed in a paediatric clinical trial program. Further, in case of chronic diseases requiring lifelong treatment for example ADHD, total duration of the treatment is longer if the treatment is started in childhood. This may expose the children to increased risk of toxicity due to accumulation of drug, for example chronic use of amphetamines and methylphenidate to treat ADHD carries the possible risk for cardiovascular events such as myocardial infarction, stroke and sudden death later in life.

2.1 Age Categories

In the PSURs as well as clinical trial reports, the data regarding paediatric population exposure are stratified according to the developmental groups taking into consideration developmental biology and pharmacology. An example of the age categories is provided in the Table below, however, this is not a perfect categorization as there is considerable overlap in developmental (for example physical, cognitive and psychosocial) issues across the age categories. Further, these groups themselves may not be homogenous for example, a 25- week gestation, new-born weighing 500 –gram is quite different from a 30-week gestation new-born weighing 1500 grams.

Age category	Age
Terms new-born infant	0 – 28 days
Infants & toddlers	>28 days to 23 months
Children	2 – 11 years
Adolescents	12 to 16 – 18 years (varies with regions)

Spontaneous reporting has only limited value in paediatric Pharmacovigilance. The paediatric population presents additional challenges in addition to the well-known limitations of spontaneous reporting. Many times, adverse events may not be detected as children have difficulty in expressing. There may not be a direct communication between the healthcare professional (HCP) and the patient, rather there is an additional step and communication is mainly through parents or caretakers.

Rate of reporting is further low due to the off-label use of medicinal products in paediatric population, as these have not been adequately tested in paediatric population. As medicinal products are used for unlicensed indications in paediatric population, there is a general hesitation on the part of healthcare practitioners to report adverse reactions associated with off-label use.

Medication errors are an important cause of adverse reactions in the paediatric population. A large proportion of medication errors are due to the incorrect calculation of dose resulting in the administration of incorrect dose leading to adverse reactions due to overdoes or lack of efficacy resulting from under-dose. These medication errors occur mainly under the off-label use as suitable paediatric formulations are not available and adult dosage formulations are adapted for paediatric use. Another reason for this may be the requirement for frequent dose calculation in this age group as weight and surface area changes rapidly due to growth and maturation. Adverse reactions associated with paediatric use are also underreported because of the potential liability issues. EMA guidance recommends that regulators and marketing authorization holders should encourage HCPs to report medication errors.

For proper recording of adverse events in paediatric age group, the participation of parents and care-givers should be encouraged by circulating educational messages directly targeted to them. Labels and pack inserts should carry information related to the safety of the medicinal products in paediatric population. Information in the label should be presented in a clear and unambiguous manner. Label should also carry information about the possibility of off-label use in paediatric population and the associated potential harm, so that parents become aware of the risks associated with the off-label use.

Quality of Reports

Like other spontaneous reports, it is important to ensure that reports submitted are of high quality. Thus, such reports should include adequate information on adverse event, concomitant medication and past-history. In addition, reports should provide accurate information on the age at the time of the onset of reaction, along with weight and height and the individual and the total daily dose. Age should be provided in completed days, months and years. In its guidance on completion of the MedWatch From 3500A, section on age, FDA recommends that if the patient is 3 years or older, use years, e.g. 4 years; if the patient is less

than 3 year old, use months e.g. 24 months; if the patient is less than one months old, use days, e.g. 5 days.

2.2 Best Pharmaceuticals for Children Act (BPCA)

To encourage and require paediatric studies, BPCA was signed into law in January 2002. This act provides six months of marketing exclusivity for a drug when a pharmaceutical company studies a drug for use in the paediatric population as requested by FDA.

Currently regulators are focusing on the off-label use in paediatric population. For all marketing applications where off-label use in paediatric population is likely, risk management plan is required in EU.

3. Monitoring the Exposure to medicinal products in pregnancy

Placental transport is established around 5th week of pregnancy, thus low molecular weight chemicals can freely diffuse across the placenta. Several chemical substances taken by the mother can potentially harm the developing foetus. While treating pregnant women the physician is required to select appropriate therapy so to alleviate the maternal suffering while taking care that no harm is done to the foetus. Apparently, one may say that conclusion can be easily drawn by comparing the maternal benefits vis a vis harm to the foetus, however, in real life this is not that simple.

For ethical reasons, it is not possible to conduct clinical trials in pregnant women. Women of child bearing age are either excluded from the clinical trials or if involved, adequate precautions are taken to avoid pregnancy. These include informing women about the fact that safety of the Investigational Medicinal Product (IMP) is not established in pregnant women and advising adequate contraception.

Animal experiments do provide some information regarding the teratogenic effects drugs.

However, there is not much information available regarding extrapolation of these findings in humans. Thus, even though the safety of a New Chemical Entity (NCE) has been thoroughly evaluated in preclinical and clinical studies; at the time of the launch of a NCE, little is known about its effects in pregnant women. In fact, the worst disaster in the history of drug development i.e. phocomelia associated with the use of thalidomide in pregnant women has been caused due to the teratogenic effect of thalidomide which could not be detected prior to its launch.

Teratogenicity refers to the capability of a product to produce fatal malformations. Such a substance is called teratogen or teratogenic agent. Traditionally teratogenic effects of drugs have been noted as anatomic malformations. Foetus is at a greater rise in the first trimester of pregnancy although chemicals can potentially cause damage to the developing foetus at other times also. It is easier to identify anatomical malformations and it is much more difficult to identify the factional and behavioural changes in the developing foetus.

Earlier, based on the information available regarding risk of reproductive and developmental adverse effects and on risk versus benefit considerations, United States food and drug administration (FDA) classified the medicinal products in Categories A, B, C, D and X. These categories do not imply an increasing progression of risk from A to X. Drugs in categories D, X, and in some cases, C. may pose similar risk, but may be categorized differently based on different risk versus benefit considerations.

On 30 June 2015, the United States Food and Drug Administration's (USFDA) Pregnancy, Lactation and Labelling Rule (PLLR) came into effect. The PLLR requires changes to the content and format for information presented in prescription drug labelling in the Physician Labelling Rule (PLR) format to assist health care providers (HCPs) in assessing benefit versus risk and in subsequent counselling of pregnant women and nursing mothers who need to take medication, thus allowing them to make informed and educated decisions for themselves and their children. The PLLR removes pregnancy letter categories – A, B, C, D and X. The PLLR also requires the label to be updated when information becomes outdated.

Generally, when a patient conceives while she is on an Investigational Medicinal Product (IMP) or marketed drug, where the risks of exposure to this medicinal product during pregnancy are not known, following actions are taken:

- Women are consulted and informed about the potential risks/ lack of knowledge about potential risk that may be caused by the drug. The physicians should not make therapeutic decisions alone. In fact, all patients including pregnant women should be involved in the decision to administer a drug by providing information available on the product.
- If the patient decides to continue the pregnancy, she / her gynaecologist is followed up regularly. Follow-up continues till one month after delivery. Details regarding baby are also recorded. They are encouraged to report adverse reactions experienced, if an or delayed milestones observed in the baby or some other untoward effects which they think may have been caused due to the exposure to the drug.

3.1 Processing the reports of drug exposure during Pregnancy

Generally, reports of exposure to a medicinal product during pregnancy without any serious adverse reactions are not to be reported on an expedited basis to regulatory authorities.

However, if there are reports of unintentional exposure during pregnancy in clinical trials, usually investigators are required to report to sponsor within 24 hours. Data on reports of exposure during pregnancy should be included in the periodic reports.

Similarly planned medical termination of pregnancy with untoward outcome is not reportable on an expedited basis, but this data should be included in the periodic reports. Report of birth defects, spontaneous abortion, late foetal death, congenital anomalies, maternal or neonatal death and other complications of pregnancy for example abruption placentae, fatal distress etc are considered reportable on an expedited basis.

Creation of parent child case:

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

- The type of report: retrospective or prospective
- Information on exposure to medicinal products during pregnancy should include dates of exposure as accurately as possible.
- Exposure to other teratogens
- The results of examinations performed: foetal ultrasound, amniocentesis, laboratory tests, etc.

If the child/foetus experiences suspected adverse reactions other than early spontaneous abortion/foetal demise:

- Information on both the parent and the child/foetus should be provided in the same report.
- This case is referred to as a parent-child/foetus report

Both the parent and child/foetus experience suspected adverse reactions other than early spontaneous abortion/foetal demise:

- Two separate reports, i.e. one for the parent (mother or father) and one for the child/foetus, should be created

No reaction is affecting the child/foetus:

- Only a parent report should be created to describe the child exposure to the medicinal product.
- The patient characteristics refer only to the parent (mother or father) who may as well experience adverse reactions with the suspected medicinal product.
- Reports with no reaction should not be submitted as ICSRs

Miscarriage or early spontaneous abortion is reported:

- Only a parent report is applicable with the patient's characteristics to be provided for the mother. However, if the suspect medicinal product was taken by the father, this information should also be recorded.

ICSR for Pregnancy exposure

Parent-child / Parent-foetus reports have been defined by FDA as those reports where a foetus/ breast feeding infant or the mother or both sustain as adverse event that is considered by the initial reported to be possibly associated with a medicinal product administered to the mother during pregnancy. Regarding reporting of the cases of exposure to medicinal products during pregnancy, regulatory authorities in general recommend that:

- Two separate reports should be prepared when both - the parent as well as the child /foetus experience adverse events. These two reports should be linked in the database as well as using the narrative.
- If there has been foetal death, miscarriage or abortion, only one report, parent report should be prepared.

If child /foetus has not experienced adverse event, only parent report should be prepared.

- Only a child report is prepared if only foetus / child experiences adverse event.

1st situation: ADR reported in mother	
Spontaneous abortion	1 case « mother »
Foetal death without information on malformation	1 case « mother »
Foetus with defects	2 cases: 1 case « mother » and 1 case « foetus » but cases linked
Birth defects or ADR in baby	2 cases: 1 case « mother » and 1 case « foetus » but cases linked
No ADR in child	1 case « mother »
2nd situation: No ADR in mother	
Spontaneous abortion	1 case « mother »
Foetal death without information on malformation	1 case « mother »
Foetus with defects	1 case « foetus »
Birth defects or ADR in baby	1 case « baby »
No ADR in child	No case
Particular situation: Twins	
One case for each twin	

Some companies prefer to enter the all case reports of exposure during pregnancy in the database, even if no adverse reactions have been reported. This helps them to retrieve the reports of exposure in pregnancy for submission in periodic reports. Some other companies may not enter such reports of pregnancy with no adverse reaction in the database but maintain such reports elsewhere for inclusion of appropriate statements on the product label.

3.2 Pregnancy Registries

Pregnancy registries are established to monitor the outcomes of pregnancies where mothers have been exposed to specific medical products by providing clinically relevant human data. US FDA defines a pregnancy exposure registry as a study that collects health information from women who take medicines or vaccines when they are pregnant. These data can then be used to appropriately update product label.

Registries can be set up by the regulatory authorities, sponsors, healthcare groups, national reporting systems and academic or research institutes. A registry helps in a systematic collection of the pregnancy outcome reports to analyse birth defects and their causal association with the medicinal product early in the life of a product. In 2002, US FDA published a guidance document for industry titled “Establishing Pregnancy Exposure Registries” to encourage the pharmaceutical industry to establish and provide guidance on how to establish pregnancy registries and providing the guidance to industry on establishing pregnancy registries.

Information about the registries is available on the Package Inserts and in Medication Guides directed to the patients. Annual reports of registries are prepared and circulated to various stakeholders. When data have been analysed and adequate conclusions have been drawn, appropriate changes may be included in the label.

Reports from registries are considered spontaneous reports. Lists of the pregnancy registries in US are available on US FDA website. These are listed by the medical condition as well as by the drug. Some of the popular pregnancy registries are Cancer and Childbirth Registry, Anti-epileptic Pregnancy Registry, Anti-retroviral Pregnancy Registry. In addition,

this website also lists useful information on participation of women in clinical trials to understand if there are gender differences in disease prevalence and the response to various therapies. FDA's Office of Women Health (OWH) was established to advocate for the participation of women in clinical trials.

4. Processing the Reports of Medication Error

Medication error refers to the inappropriate use of medication. Medication errors include prescribing, dispensing as well as administration errors. Medication errors include incorrect drug, incorrect does, inappropriate schedule, dose omission, under dose, overdose, co-administration of drugs that interact with each other, incorrect route of administration or administering drugs in patients where contraindicated for example allergies to certain ingredients and medical conditions.

Latent medication errors refer to those medication errors that were identified and corrected before drug administration. For example, the pharmacist dispensed the wrong medication, however, this was noted by the patient who has been regularly taking the same medicine as incorrect prescription was noted prior to administration of the drug, medication error was corrected prior to the drug administration; hence this is termed as 'latent medication error'.

Medication errors can lead to adverse reactions. Medication errors are different from other adverse reactions as these are preventable. Therefore, it is important to learn about the causes of medication errors, processing of the reports of medication errors and how these can be prevented.

Medication errors can occur at the level of the physician, pharmacist, nurse or the patient himself. Prescribing errors may occur at the level of the pharmacist, physician or nurse. Although it appears that dispensing errors would be limited to the pharmacists, however, this is not the case as drugs may be dispensed in physician's office also, for example sample products.

Some of the common causes of medication errors includes:

- Poor handwriting
- Confusion of dosing units for example 0.5 mg of written without the preceding zero(.5mg) may be misinterpreted as 5 mg leading to overdose administration of 10 times of prescribed dose.

- Incorrect product labeling –drugs are usually packaged into smaller units in pharmacies. Inappropriate labeling of smaller units can lead to serious medication errors.
- Updated package inserts are not included.
- Incomplete information about the patient, for example patient's allergies, concomitant medications taken by the patient leading to drug interactions.
- Errors of reconstitution and storage are also common, for example storage of drugs in the wrong compartment of the refrigerator, leaving vials outside the refrigerator, not consuming (or discarding) the reconstituted vials within advised duration.
- Inappropriate or confusing abbreviation for example abbreviation PTU is used for Propylthiouracil, however, it may be misinterpreted as Purinethol, abbreviation MTX used for Methotrexate is mistaken as Mitoxantrone.
- Confusion between drugs with similar names, for example Sumatriptan and Sitagliptin.

Medication errors include confusion regarding the name of the drug resulting in the administration of the wrong drug, therefore, regulatory authority pay adequate attention towards the nomenclature of medicinal products both brand and INN names. Some recent example include confusion in the name of Kapidex and Casodex.

To prevent the medication errors, FDA approved the change of brand name for Kapidex (Dexlansoprazole) to Dexilant. Another example of confusion between the names resulting in adverse events includes Carac (Flurouracil Cream) and Kuric (Ketoconzole cream).

Medication errors can seriously impact the benefit risk profile of drugs. There were reports of paediatric overdose due to confusing labeling / packaging of Arginine hydrochloride injection (R-Gene 10), therefore, revisions were made to the product labeling, container labeling and packaging configuration. Some other examples of overdose due to labelling confusion include Nitrostate (Nitroglycerine) and Seroquel (Quetiapine).

Medication errors are reportable events and FDA/ CDER medication error division works closely with the Institute for Safe Medication Practices (ISMP) on issue related to medication errors.

5. Reports of abuse, misuse, occupational exposure

Reports of abuse/misuse/occupational exposure

- With no associated suspected adverse reaction should not be submitted as ICSRs.
- Reports associated with suspected adverse reactions should be subject to submission

Along with the resulting suspected adverse reactions, an appropriate MedDRA LLT term corresponding most closely to the description of the reported overdose, abuse, off-label use, misuse, medication error or occupational exposure should be specified in the ICH-E2B section 'Reactions/Events'.

5.1 Off-label use versus medication error and misuse

Medication errors should be clearly distinguished from off-label use.

Off-label use relates to situations where the medicinal product is intentionally used for a medical purpose not in accordance with the authorised product information. Medication error however refers to any unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient.

Medication errors should be clearly distinguished from misuse.

Misuse relates to situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorised product information.

For cases where a patient has misunderstood the instructions for how to use the medicine correctly, this should be considered an error and appropriate MedDRA terms selected to represent the event, e.g. LLT Tablet crushed incorrectly.

5.2 Special situation: Overdose/under dose versus medication error

Overdoses are not necessarily considered to be medication error unless unintentional overdose occurred as a consequence of an error. In this situation it is important to code both concepts to facilitate case identification.

Intentional overdose is not considered a medication error.

For the purposes of term selection and analysis of MedDRA-coded data, Overdose means more than the maximum recommended dose (in quantity and/or concentration), i.e. an excessive dose, whereas under dose is the administration of less than the minimum recommended dose (in quantity and/or concentration).

Both over- and under dose may unintentionally be the result of a preceding medication error and relevant terms from the HLT Maladministration may be chosen in combination with the associated medication error term.

5.3 Special situation: Product quality issue versus medication error

Product quality issues are abnormalities that may be introduced during the manufacturing, labelling, packaging, shipping, handling or storing process of a medicinal product. They should be distinguished and carefully evaluated if they fall in the definition of a medication error.

For example, an under dose of antibiotic was administered because the lines on the dropper were hard to read which led to a medication error (accidental under dose). Medication errors involving a drug delivery device may be related to wrong use of the device with clinical consequence for the patient related to the drug.

The HLT Maladministration contains terms for errors associated with drug delivery devices. Other terms in the HLGT Device issues may be relevant as appropriate.

6. Special situation: Lack of efficacy (LOE)

Lack of efficacy should be considered as expected because no drug is expected to be 100% effective in all patients. Reports of lack of therapeutic efficacy should be collected and recorded when notified and followed-up if incomplete.

They should normally not be submitted as ICSRs if there is no associated suspected adverse reaction, but they should be discussed in periodic safety update reports as applicable.

In certain circumstances, reports of lack of therapeutic efficacy with no suspected adverse reactions may require to be submitted within a 15-day time frame:

- If single cases give rise to the suspicion of product related issues (e.g. counterfeit).
- Medicinal products used for the treatment of life-threatening diseases
- Vaccines
- Contraceptives

The ICSRs should be submitted within a 15-day time frame even if no seriousness criterion is specified.

Progression of an underlying disease, when reported and qualified for entry as an Adverse Event, should be considered unexpected/unlisted unless it is specifically described in the reference safety information. Unless aggravation of the medical condition occurs, the indication for which the suspected medicinal product was administered should not be included in the ICH-E2B section 'Reactions/Events'. If the primary source suspects a lack of therapeutic efficacy, the MedDRA LLT term, corresponding most closely to the description of the reported lack of therapeutic efficacy, should be specified in the ICSR.

7. Specific situation: Interaction

For the event of drug interaction to be considered as expected/listed, the drug interaction should be described in the appropriate section of the labelling document together with the second suspect drug or drug class. The symptoms attributed to the interaction are expected if they are clearly noted as expected/listed in the drug interaction section or other appropriate sections.

Events mentioned in the interaction section should only be considered expected/listed if the patient received both specified drugs.

8. Suspected Transmission of Infectious Agents via a Medicinal Product

All reports of Suspected Transmission of Infectious Agents via a Medicinal Product (STIAMP) should be processed as medically significant, unless another serious criterion is applicable, and unexpected/unlisted in all labelling documents.

if the infectious agent is specified in the report, the MedDRA LLT term corresponding most closely to the infectious agent should also be included in the ICSR.