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GUIDELINE ON CONDUCT OF PHARMACOVIGILANCE FOR MEDICINES USED BY THE PAEDIATRIC POPULATION

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GUIDELINE ON CONDUCT OF PHARMACOVIGILANCE FOR MEDICINES USED BY THE PAEDIATRIC POPULATION

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1 INTRODUCTION (BACKGROUND)

The paediatric population is defined in the European Union as those persons aged between 0 and 18 years. Many medicines are prescribed to the paediatric population on an unlicensed or 'off-label' basis, because they have not been adequately tested and/or formulated and authorised for use in appropriate paediatric age groups. There are moves to address this situation. A number of initiatives at national and regional levels aim to stimulate paediatric medicines development and increase the availability of appropriately formulated, properly tested medicines authorised for paediatric use and to improve the paediatric information available for products not authorised for paediatric use. The conduct of pharmacovigilance for medicines used by the paediatric population needs to be addressed in this context.

2 SCOPE

This guideline is directed towards marketing authorisation holders and competent authorities. It is also of relevance to all those involved in the conduct of paediatric clinical trials. It applies to 'off-label' and unlicensed as well as licensed use. It does not address the paediatric use of vaccines. A separate CHMP Guideline on the Conduct of Pharmacovigilance for Vaccines is under development.

The ICH Note for Guidance (CPMP/ICH/5716/03) provides the basic guidance for planning pharmacovigilance activities. This guideline aims to clarify and emphasise the particular aspects of pharmacovigilance and risk minimisation that are relevant for the paediatric population.

3 THE ROLE AND RESPONSIBILITIES OF DIFFERENT STAKEHOLDERS

Stakeholders in the process of paediatric pharmacovigilance include the paediatric population and their parents/carers, regulatory authorities, the pharmaceutical industry, health professionals, patient organisations, national health care systems and the media.

Although the degrees of responsibility differ between the groups, all stakeholders have an important role in contributing information in this process and in ensuring that paediatric pharmacovigilance is maximally effective, fully assessed and, through responsibly communicated risk reduction strategies, results in the safest use of products in the paediatric population, irrespective of authorisation status. The participation of parents and caregivers is crucial and should be encouraged by directly targeted educational messages from the regulatory authorities. The co-operation of these groups is integral to securing long-term follow-up for adverse reactions that may become apparent only after months or years. Regulatory authorities also need to remind health professionals of the importance of their contribution to the process of paediatric pharmacovigilance through their reporting of adverse drug reactions (ADRs). Perhaps the greatest responsibility lies with the marketing authorisation holders who plan and implement pharmacovigilance activities and the regulatory authorities who approve and oversee them and assess the outcomes. In addition these two groups are primarily responsible for the timely, sensitive communication of new paediatric safety information to the health professionals and the general public.

4 SPECIAL CHARACTERISTICS OF PAEDIATRIC PHARMACOVIGILANCE

The conduct of pharmacovigilance for medicines for paediatric use requires special attention. Childhood diseases and disorders may be qualitatively and quantitatively different from their adult equivalents. This may affect either the benefit or the risk of therapies (or both), with a resulting impact on the risk/benefit balance. Chronic conditions may require chronic treatment and the susceptibility to ADRs may change throughout the patient's life-time according to age and the stage of growth and development. This is especially true for effects on the central nervous system. Growth and development during childhood reflect many underlying and interrelated processes. An interaction with these may result in ADRs not seen in the adult population, irrespective of the duration of treatment. In

addition, the associated rapid changes in body mass, morphology and composition may present additional challenges in identifying and selecting the optimum dosing regimen.

The lack of reliable data in paediatric populations is associated with particular problems including:

- limited available safety data due to lack of clinical trials in the paediatric population;
- under- or over-dosing in some age groups due to lack of pharmacokinetics data or dose-finding studies
    - under-dosing may result in lack of benefit or development of resistance
    - over-dosing may result in an increase of Type A reactions
- inadequate capture of events arising in the paediatric population from routinely available safety data
- incorrect dosing, use of products of less controlled quality or inappropriately high local concentrations leading to local adverse reactions due to lack of age-appropriate formulations ;

Safety data in the paediatric population cannot necessarily be extrapolated from data in adults because certain ADRs may only be seen in the paediatric population depending on the maturation of organ systems (e.g. skin, airways, kidney, liver, blood-brain-barrier), metabolism, growth and development. In particular:

- the pharmacokinetics and pharmacodynamics of a compound may be different in the paediatric population compared with adults and the former may be particularly vulnerable to ADRs or have different drug interaction profiles;
- the paediatric population may be more susceptible to ADRs from specific excipients;
- different ADRs may be relevant for different paediatric age groups and specific pharmacovigilance plans, strategies and activities should be tailored accordingly. In utero exposure may represent an additional risk factor;
- due to maturation, growth and development in the paediatric population may be susceptible to drug-induced growth and developmental disorders, as well as to delayed ADRs not seen in adults. Long term follow-up data may be necessary to detect such effects;
- drug-induced “programming” may occur i.e. permanent effects may result from a drug exposure at a sensitive point in development (‘critical window’), this is a particular consideration in foetal or neonatal life;
- certain ADRs may only be seen in the paediatric population, irrespective of effects on growth and development;
- in the case of life-long treatments for chronic diseases, the total duration of treatment is longer if started in childhood. This may expose the patient to increased risks of developing an ADR.

The problems are accentuated when the drugs involved are not authorised for paediatric use:

- unlicensed medicines or medicines used ‘off-label’ may have inadequate product information to support safe paediatric use;
- underreporting of adverse reactions may occur in relation to unlicensed or ‘off-label’ use due to legal and liability concerns.

In addition, children may be unable to communicate adverse reactions clearly to their carers/ health care professionals or may not be aware of the adverse reactions as such.

Premature babies may be at a much higher risk (for example due to slow elimination of xenobiotics, distribution barriers, physiological regulatory functions and “imprinting”) and therefore need enhanced pharmacovigilance.

5 CLINICAL SAFETY AND PHARMACOVIGILANCE BEFORE AUTHORISATION OF A PAEDIATRIC INDICATION

Pharmacovigilance measures should be assessed at all stages of a product life cycle. Paediatric pharmacovigilance assessment may be rather limited before authorisation as there are often relative deficiencies in pre-authorisation clinical trials of medicines for paediatric use. Sample sizes in Phase I and II trials are usually low and even in phase III trials sample size calculations are nearly always based on efficacy assumptions. That means that the sample size limits the ability to observe anything less frequent than common reactions.

Serious adverse reactions are often rare, and are generally not observed in the paediatric clinical trial programme, particularly if there is a latent period before onset or a trigger such as a change in growth or development. For most medicines it will be impossible to fully investigate rare adverse reactions prior to authorisation, as it is necessary to expose a large number of subjects to a medicinal product to elicit a reaction which occurs with a low probability in the target population.

An additional constraint is that for many conditions the target paediatric population will be relatively small. And there may be a number of distinct age ranges to be considered within the target paediatric population.

Given these limitations, every opportunity should be taken to maximise the information obtained from the occurrence of an ADR during the paediatric development programme. Clinical trial protocols should set out, by category of ADR, the actions to be taken and their timing should an ADR occur . For example, should a serious ADR occur, a blood, saliva or urine sample should be taken, as appropriate, as soon as possible after the event and frozen for drug and metabolite measurement. It may also be appropriate to include similar provisions in post-authorisation safety studies. It is acknowledged that including such a provision in a trial protocol would disqualify the trial from having non-interventional status.

The safety specification and pharmacovigilance plan should highlight areas where data are lacking (i.e. safety has not been demonstrated). This should reflect duration of use, patient numbers, both overall and in the different age categories, and indications studied. It should highlight potential risks for using the medicines in the paediatric population and suggest both post-authorisation safety data collection mechanisms (e.g. post-authorisation safety studies) and risk reduction strategies (see Pharmacovigilance Planning (PVP) ICH Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03)). Proposals for prospective monitoring will depend on the size of the target population.

Special consideration should be given to the need for long-term follow up, for example, through treatment registries, including possible effects on skeletal, neural, behavioural, sexual and immune maturation and development. This may be informed by juvenile animal toxicology studies, although the predictive value of such studies in terms of subsequent effects in the paediatric population is currently unknown. (See ICH M3 (R1) Note for Guidance on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals (CPMP/ICH/286/95-)- section 11, ICH E11 Note for Guidance on the Clinical Investigation of Medicinal Products in the Paediatric Population (CPMP/ICH/2711/99)– section 2.1, ICH S5 (R2) Note for Guidance on the Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility (CPMP/ICH/386/95) - note 17). Mutagenicity and carcinogenicity data are also relevant in this context.

Pharmacogenomics/pharmacogenetics is an important emerging area. Consideration should be given to the use of pharmacogenomic/pharmacogenetic methodology to predict risk and to monitor adverse reactions prospectively. For example, evidence suggests that the risk of myelosuppression induced by 6-mercaptopurine or azathioprine during treatment of some childhood leukaemias is much higher in patients with genetic deficiency of S-methyl thiopurine transferase. In this respect, consideration should be given to the storage of blood or saliva for DNA analysis. Appropriate consent will be required.

Whenever a medicinal product is likely to be used in the paediatric population, the EU Risk Management Plan (EU-RMP) that forms part of the application for marketing authorisation should address specific paediatric issues. The Pharmacovigilance Plan (PP) should include a paediatric section and, where appropriate, specific paediatric risk minimisation activities should be included in a risk minimisation plan. The specific paediatric proposals should be based on relevant epidemiological data regarding the prevalence of disease in the appropriate paediatric age groups. The data informing risk predictions will come from preclinical studies, trials in both the adult and paediatric populations and post-authorisation trials.

An EU-RMP addressing paediatric issues should be requested whenever a safety specification suggests safety concerns or potential safety concerns, or where data are limited or for other reasons identified by the regulators. There should be particular emphasis on 'off-label' use, medication errors and reports of poisoning. Plans to extend the paediatric indication post-authorisation should also be taken into consideration. If there is particular cause for concern, it is a condition for granting marketing authorisation for any application including an indication for paediatric use that a risk management system be set up or that specific post-marketing studies be performed and submitted for review.

6 PHARMACOVIGILANCE FOR PRODUCTS ON THE MARKET (INCLUDING 'OFF-LABEL' USE)

6.1 General issues

In most cases paediatric clinical trial data are likely to be limited at the time of initial product authorisation, whether or not the condition is common in the paediatric population and whether or not the medicinal product is authorised for paediatric use. In addition there may be a number of distinct age groups of relevance within the target paediatric population. Paediatric pharmacovigilance is therefore particularly important during this period.

In the case of products of low usage in the paediatric population, the mechanisms for detecting new safety signals with extensively used drugs (like spontaneous reporting systems) may be much less effective. A different, more proactive, approach is needed to conduct pharmacovigilance for low usage products, for example use of disease databases and active surveillance systems. Sentinel sites[1], specialist networks and paediatric clinical trial networks may be equally useful in this context.

Where unlicensed and 'off-label' paediatric use is common, it is important for both the marketing authorisation holder and the regulatory authorities to monitor for any consequential safety concerns and to take appropriate measures to address them.

6.2 Specific issues

In addition, there are specific issues to consider at different points in the pharmacovigilance process when dealing with medicines for the paediatric population. Data collection is emphasised as this is considered to be critical.

6.2.1 Data Collection

Methods of obtaining reports should be appropriate for the age category under study, for example, spontaneous reports, elicited reports, questionnaires. Lay and professional enquiries to the marketing authorisation holder (MAH) or to the regulators can also be an important source of signals.

Spontaneous reports

Effective pharmacovigilance requires the efficient capture of data relevant to the safety of medicines. Such data are used for both signal detection and signal evaluation. Spontaneously reported suspected

[1] See section 7 Definitions

adverse drug reactions remain the most important source of detecting safety issues in the post-authorisation phase. However, the paediatric population presents extra challenges in addition to the well-known limitations of spontaneous reporting systems. Children may be unable to or have difficulty in expressing problems that may therefore go undetected. In addition parents/carers present an added step before a report of a suspected ADR can reach the regulator. Another relevant factor is the reluctance of a health professional to report a suspected ADR if a medicine is being used on an 'off-label' or unlicensed basis because of possible liability issues. MAHs and competent authorities should encourage reporting of all suspected ADRs, whether they occur in the context of licensed or 'off-label' or unlicensed use. In the case of reporting in the context of "off-label" or unlicensed use or a medication error, competent authorities may wish to provide explicit reassurance that the personal data regarding the reporter will be protected.

Unless the reluctance to report can be overcome, spontaneous reporting is expected to be of only limited value in paediatric pharmacovigilance monitoring. Different groups of reporters should be engaged in a collective effort to overcome the underreporting of suspected paediatric ADRs. Groups include regional pharmacovigilance centres, national patient safety agencies, community and hospital pharmacists, poison centres, learned societies and patients/parents/carers. In order for this to have a useful impact, the regulatory authorities should emphasise the importance of reporting to prospective reporters through targeted, structured campaigns. These should include information on what to report, how to report it and the extent to which the identity of the reporter will be protected. The quality of information in the reports is particularly important in order to assess the effect of dose. Accurate information on precise age at the time of the adverse reaction (corrected if preterm) in completed days, months and years, weight, height, dose (including individual and total daily dose), relevant past medical history, other drugs and onset of reaction should all be reported. Families and carers should be encouraged to report adverse reactions to health professionals. In some Member States it is possible for the patients/carers to report directly to the regulatory authorities. Reporting should be simplified (e.g. electronic as well as paper) and made target user friendly.

The awareness and motivation of health professionals may be improved by:

- Communication and general training
- Provision of user-friendly feedback
- Work with learned societies and specific paediatric research networks
- Better collaboration with paediatric hospital units (including neonatology units)
- Greater involvement of paediatric pharmacologists in oversight of paediatric in-patients

Medication errors are an important cause of paediatric adverse reactions. They are often associated with the use of adult dosage strengths or adaptation of an adult formulation for paediatric use where no suitable paediatric formulation exists and are probably underreported because of possible liability issues. As for unlicensed and off-label use, MAHs and competent authorities should encourage reporting of all suspected ADRs occurring in the context of a medication error and should provide reassurance that the identity of the reporter will remain confidential. The reporter should indicate clearly that the adverse reaction has occurred as a result of a medication error, and should include details of the formulations involved and information on any manipulations made to the product by medical, nursing or pharmacy staff. In some Member States the reporting of medication errors is separate from the reporting of ADRs. Where this is the case the medication error reports should be obtained and analysed.

Targeted Active Data Collection

Active surveillance units provide a way of addressing the particular problem of under reporting of spontaneous paediatric data. The MAH will be primarily responsible if the activity is part of a pharmacovigilance plan or post-authorisation commitment but the units may be supported by the industry or by the public sector. They may be based within professional bodies, learned societies,

institutions or networks including regional pharmacovigilance centres, poison control centres, primary or community care networks and paediatric clinical trial networks and may target professional groups such as paediatricians (hospital-, university- or community-based), paediatric pharmacists or medicines information centres. They may make use of disease or treatment registries or national databases. Combined data recording with primary and secondary care data linkage is important for conditions commonly managed jointly by primary and secondary care. The aim is to actively solicit reported adverse drug reactions on a regular basis. This may be in relation to all medicines, groups of medicines or individual medicinal products. It may be more useful in the context of highly novel therapies, as part of a strategy to manage known risks or where the potential for long-term toxicity is of particular concern. An appropriate control group should be considered for inclusion in follow-up evaluations. Although early reports are encouraging, the overall effectiveness and contribution to paediatric pharmacovigilance of targeted active data collection has still to be established. In all cases regulatory authorities should make it clear that the solicited reports are treated confidentially.

Because of the small number of children in any one database, the real value of such data may only be appreciated when the information is pooled, either using formal systematic analysis or informal review.

Periodic Safety Update Reports (PSURs)

These key public health documents are produced by the marketing authorisation holder as required by European legislation. The content and format is set out in the ICH E2C (R1) Note for Guidance on Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs (CPMP/ICH/288/95) and Addendum (CPMP/ICH/4679/02).

If there is a paediatric indication, if there is evidence of significant 'off-label' use or if there are adverse reactions reported in the paediatric population, then the use in the paediatric population should be considered specifically and discussed in a separate section in the PSUR. Data from completed or ongoing clinical trials should be presented separately from spontaneous reports. The report should explicitly address any new safety issue in the paediatric population overall as well as by age group and indication.

Paediatric population exposure should be broken down according to ICH age groups or, if justified, by other developmentally meaningful groups. Detailed information on the pattern of use of medicinal products in the paediatric population should be provided systematically by MAHs based on, for example, drug utilisation studies (including detailed information on 'off-label' use and dose, broken down by age or other developmentally meaningful categories).

The addition of a paediatric indication to an existing EU marketing authorisation requires the submission of 6 monthly PSURs for the following two years. These should focus on paediatric use. Thereafter the periodicity of the PSUR submission should be phased in with the PSUR submission schedule already in place, (see Volume 9A).

Published literature

This is another important source of safety data. The MAH should conduct a thorough search of the literature for reports of ADRs in the paediatric population. Literature searches may also reveal non-MAH sponsored clinical trials which yield important safety information. Meta-analysis of clinical trials and epidemiology data can also be helpful.

Post authorisation safety studies

These fall into three broad categories:

I. those designed to demonstrate safety (large numbers of patients studied to expand the safety database)

II. those designed to detect new safety issues (hazard detection)

III. those designed to evaluate known safety issues (eg those detected in the pre-authorisation phase)

They may be conducted by academics, marketing authorisation holders or the regulatory authorities. The study population may be in primary, secondary or tertiary care. The rules applying to non-interventional studies[2] are set out in Volume 9 of the Rules Governing Medicinal Products in the EU, whereas all other post-authorisation safety studies fall within the scope of Directive 2001/20/EC.

Guidance on when such studies should be conducted is given in the ICH Note for Guidance on Planning Pharmacovigilance Activities (CHMP/ICH/5716/03) and in the EU guideline on Risk Management Systems for medicinal products for human use (EMEA/CHMP/96268/2005). Decisions should be made on a case-by-case basis and based on knowledge of the limitations of pre-approval database and the known or potential risks. The annexes to both notes for guidance mentioned above give advice on the types of study available. In terms of the paediatric population the ethical issues, study design and study conduct require special consideration. It is essential that paediatricians and/or paediatric pharmacologists are involved in the study design and conduct. In addition it may be helpful to involve patient representatives and primary care physicians where relevant.

Specific methodologies are needed to detect long-term, delayed and developmental ADRs. For example, specialised disease (or other) registries and drug prescription databases can capture safety information prospectively provided that specific clinical questions are established from the outset so that the relevant data can be collected. When using these databases care is needed regarding the data quality review processes, including definitions of critical events and their timing. The age should be recorded in completed days for neonates, days and months for infants and toddlers and completed years and months for children and adolescents. Users should also try to estimate the degree of underreporting and of correct case ascertainment. Links between registries should be explored and exploited where possible. Population-based cohort and case-control studies and analyses of epidemiological databases should also be considered.

Tools to investigate rare adverse reactions via the establishment of an active post-marketing surveillance programme include post-marketing surveillance studies, ad hoc epidemiological studies, use of large databases linking treatment and medical outcome, registries and laboratory investigations. Meta-analysis of different studies for identification of rare adverse drug reactions should also be considered. Safety evaluations in clinical trials should be standardised to facilitate the assessment of rare adverse reactions across clinical trials. In addition, a population pharmacokinetic approach could be built into a post authorisation safety trial using sparse data collection, according to the PK profile of the drug.

6.2.2 Data Management

The data should be managed in a form that allows reproducible data retrieval and analysis by age and indication. It is essential that the database is stratified for age and that age is coded as accurately as possible (preferably as date of birth and date of observation). If only age is used, it should be recorded in completed days for neonates, days and months for infants and toddlers and completed years and months for children and adolescents. The gestational age of the child at birth should be recorded for ADRs occurring in the neonatal and early infant period. Information on major developmental parameters (prematurity, pubertal development) should also be recorded. For early identification of new adverse drug reactions it is also essential that all relevant data are accurately reported and collected in one location with minimal delay. A model for electronic collection of safety data related to products recently authorised in the EU has been developed by the European Medicines Agency. It is planned that this EudraVigilance system will cover all medicinal products authorised in the EU and will enhance the value of spontaneous reporting of adverse drug reactions. Through the data analysis tools in EudraVigilance it should be possible to run regular customised queries to detect paediatric ADRs (for instance those related to growth, development, sexual maturation).

[2] See section 7 Definitions

6.2.3 Signal Detection

A drug safety signal may arise from a previously unrecognised safety issue, a change in the frequency or severity of a known safety issue or identification of a new at risk group. These are all relevant in the paediatric population and both the MAH and the regulatory authorities are responsible for making sure that systems and processes are in place so that they can be addressed.

For the most part, both signal detection and data mining in the paediatric population depend on the detection methods used being effective for small populations and low numbers of possible cases. Enhanced data capture techniques can increase the completeness of the information obtained. Signal detection is also of great importance in the calculations used for statistical signal detection tools such as proportional reporting ratios (PRRs)[3].

Statistical methodologies are available to stratify by age group and can be helpful in increasing the ability to detect signals from spontaneous databases. However, signal detection is an evolving field and the most up-to-date suitable statistical methodologies should be used.

Signal detection should be focused within each paediatric age category and also applied to the paediatric population as a whole. Because the number of events is usually small there should be a high index of suspicion, careful scrutiny of individual cases and an emphasis on follow-up to obtain essential information. One case report may be enough to trigger an investigation.

The detection of delayed or chronic toxicities including effects on growth and development presents particular difficulties. The need for long-term follow up should be considered on a case-by-case basis. When the safety issue is predictable long-term follow up, registries, or long term cohort studies should be considered.

6.2.4 Risk Evaluation and Benefit Risk Assessment

As stressed in the CIOMS IV Working Group report on benefit risk assessment, all populations and indications should be assessed for benefit and risk during a benefit-risk assessment. Long-term benefit-risk and available comparative therapies should also be taken into account, as well as the benefit-risk in adults. When considering a benefit risk assessment of medicines used by the paediatric population it is necessary to obtain an estimate of exposure in order to calculate the level of risk. Guidance on how to estimate ‘off-label’ use is given in the next section. There is also a need to involve relevant expertise, including independent expert advice. The benefit-risk assessment may be different for the use of the product in different paediatric indications. In addition this may be influenced by the availability of different therapeutic options.

6.2.5 Regulatory Action

The regulatory and risk reduction tools that are available for medicines authorised for use in adults may be not be available when such medicines are used on an ‘off-label’ or unlicensed basis in the paediatric population.

In the case of an overriding safety concern relating to an unlicensed medicine, regulatory options may be limited to prohibiting the importation of the unlicensed medicine on safety grounds, although the situation may differ from Member State to Member State. Other possibilities might be to only allow import of the unlicensed medicine on condition that paediatric use is within a clinical trial setting or entered on a clinical register. These regulatory options, however, do not apply to unlicensed medicines that are extemporaneous formulations.

‘Off-label’ use is, by definition, outside the terms of the marketing authorisation and therefore difficult to regulate. MAHs are not allowed to promote ‘off-label’ use and regulatory authorities need to be vigilant to ensure that this does not happen. The MAH should monitor ‘off-label’ use of a product in

[3] Evans SJ, Waller PC, Davis S Pharmacoepidemiol Drug Saf. 2001 Oct-Nov;10(6):483-6

the paediatric population by indication and actively collect safety data relating to such use, for example using medical records, general practice databases, hospital prescribing databases or sentinel sites, drug reimbursement schemes, or by performing targeted drug utilisation studies. MAHs should encourage prescribers to report ADRs associated with 'off-label' or unlicensed, as well as licensed, paediatric medicines use. According to Article 8.3 of Directive 2001/83/EC a marketing authorisation holder (MAH) is under an obligation to update the information submitted in support of a marketing authorisation application, including information in relation to therapeutic indications, contra-indications and adverse reactions. This applies to paediatric use whether it is on- or 'off-label'. So if important safety information relating to 'off-label' use becomes available, this should be introduced into the summary of product characteristics. The reasons for a relative or absolute contraindication should be presented in the product information so that a prescriber (and parent/carer or patient) is informed of the risk assessment of 'off-label' use.

6.2.6 Communications

The product information should describe paediatric safety issues in accordance with the Notice to Applicants Guideline on the Summary of Product Characteristics. This should not be confined to authorised paediatric indications but should reflect the use of the product and current knowledge. Any recommendations not to use the product in children or any relative or absolute contraindications should be explained, particularly in terms of the availability (or lack) of data. The aim is to provide clear, unambiguous, non-alarmist information which enables risk-minimisation and informs decision-making. The patient information leaflet should state clearly that in certain circumstances a prescriber may prescribe a medicine that is not authorised for use in children, but that this is done on the basis of the best available information and in the best interests of the child. Where appropriate, child-friendly information should be included in the patient information leaflet, in a separate section if necessary. It may be appropriate to provide different information for different age groups and to present such information differently. A question and answer format may be helpful for older children and adolescents.

Once a product is marketed for paediatric use more safety information will become available. Much of this will be communicated in the product information, but there will be times when it is important to reach a wide audience of parents/carers, patients and health professionals and to a different time scale. This may be undertaken by the MAH or the regulatory authority or both depending on the situation. In addition to fulfilling the requirements of Article 104(9) of Directive 2001/83/EC, communications should be coordinated so that a coherent message is sent out. Such communications may be routine or urgent and appropriate routes of communication should be used accordingly. The communication of safety issues arising from 'off-label' or unlicensed use requires careful handling. A number of different messages may need to be conveyed. These include a clarification of the regulatory status, the fact that a health professional may prescribe an unlicensed or 'off-label' medicine on his/her own responsibility in the best interests of the patient, the safety issue itself and the advice for risk-minimisation.

6.2.7 Audit and Outcome Assessment

As is good practice in all areas of pharmacovigilance, there is a need to ensure effective audit of the pharmacovigilance process and measurement of the outcomes of any actions taken.

7 Definitions

For definitions of pharmacovigilance–related terms please see Volume 9A of the Rules Governing Medicinal Products in the European Union, Volume 9A.
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev9.htm

Sentinel site: see Annex A of the Guideline on Risk Management Systems for Medicinal Products for Human Use (EMEA/CHMP/96268/2005)

Non-interventional study: see Directive 2001/20/EC

8 References (Scientific or legal)

This guideline should be read in conjunction with:

- Rules Governing Medicinal Products in the European Union, Volume 9A (Pharmacovigilance)
- ICH E11 Note for Guidance on the Clinical Investigation of Medicinal Products in the Paediatric Population (CPMP/ICH/2711/99)
- EWP Guideline on Clinical Trials in Small Populations (CHMP/EWP/83561/2005)
- ICH E2C (R1) Note for Guidance on Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs (CPMP/ICH/288/95) and Addendum (CPMP/ICH/4679/02)
- ICH E2E (PvP) Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03)
- CHMP Guideline on Risk Management Systems for Medicinal Products for Human Use (EMEA/CHMP/96268/2005)
- ICH E2D Post Approval Safety Data Management: Note for Guidance on Definitions and Standards for Expedited Reporting (CPMP/ICH/3945/03)
- CHMP Guideline on the Exposure to Medicinal Products during Pregnancy: need for Post-Authorisation data (EMEA/CHMP/313666/2005)
- Discussion Paper on the Impact of Renal Immaturity when Investigating Medicinal Products Intended for Paediatric Use (CPMP/PEG/35132/03)
- CHMP Concept Paper on the Impact of Liver Immaturity when Investigating Medicinal Products for Neonatal Use (EMEA/CHMP/PEG/194605/2005)
- CHMP Concept Paper on the Impact of Lung and heart Immaturity when investigating medicinal products intended for Neonatal use (EMEA/CHMP/PEG/114218/06)
- Concept Paper on the Impact of Brain Immaturity when investigating medicinal products intended for Neonatal use (EMEA/181377/2006)
- CHMP Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: from Data to Labelling (EMEA/CHMP/203927/2005)
- CHMP Guideline on the need for Non-Clinical Testing in Juvenile Animals on Human Pharmaceuticals for Paediatric Indications (EMEA/CHMP/SWP/169215/2005)
- ICH M3 (R1) Note for Guidance on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals (CPMP/ICH/286/95)
- ICH S5 (R2) Note for Guidance on the Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility (CPMP/ICH/386/95)
- Rules governing Medicinal Products in the European Community, Notice to Applicants, Volume 2C - “A Guideline on the Summary of Product Characteristics”
- Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (Official Journal L 121, 1/5/2001 p. 34 – 44, Corrigendum Official Journal L 300, 5/11/2002 p. 58 - 58 NL)

- Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medical products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC Official Journal L378, 27/12/2006, p. 1-18 and Regulation (EC) No 726/2004 and Regulation (EC) No 1902/2006 of the European Parliament and of the Council of 20 December 2006 amending Regulation 1901/2006 on medicinal products for paediatric use (Official Journal L378, 27/12/2006 p. 20-21)

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