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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

This guideline should be read in conjunction with Volume 9 of the Rules Governing Medicinal Products in the European Union (Pharmacovigilance), the CPMP Note for Guidance on the Clinical Investigation of Medicinal Products in the Paediatric Population (CPMP/ICH/2711/99), the CHMP guideline on Clinical Trials in Small Populations (CHMP/EWP/83561/2005 – in development), the CPMP Note for Guidance on Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs (CPMP/ICH/288/95), ICH Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03), the CPMP Note for Guidance on Definition and Standards for Expedited Reporting (CPMP/ICH/3945/03), the CHMP Draft Note for Guidance on the Exposure to Medicinal Products during Pregnancy (EMA/CHMP/1889/04/consultation), the Discussion Paper on the Impact of Renal Immaturity when Investigating Medicinal Products Intended for Paediatric Use (CPMP/PEG/35132/03), the CHMP Draft Concept Paper on the Impact of Liver Immaturity when Investigating Medicinal Products for Neonatal Use (EMA/CHMP/PEG/194605/2005), the CHMP Draft guideline on the Risk Assessment of Medicinal Products on Human Reproductive and Development Toxicity: from Data to Labelling (CPMP/SWP/373/01), the CHMP Draft Guideline on Risk Management Systems for Medicinal Products for Human Use (CHMP/96268/2005 - in development), the Notice to Applicants guideline on the Summary of Product Characteristics, and Directive 2001/20/EC of the European Parliament and of the Council 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. Although all of the above texts are important, the ICH Note for Guidance (CPMP/ICH/5716/03) on Planning Pharmacovigilance Activities is the key text in relation to this document.

The guideline is directed towards marketing authorisation holders and competent authorities. 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) should be read as the basic text 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.

2 BACKGROUND

The paediatric population is defined in the European Union as those 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.

3 CONSIDERATION OF DIFFERENT PRODUCT TYPES

The decision to use a medicine to treat a child with a disease (or to prevent a disease) requires an evaluation of the benefit risk balance for that intervention in that child. The level of safety expected of a medicine will depend on the disease being treated or the frequency and seriousness of the disease being prevented.

Certain paediatric conditions are rare and medicines developed for their treatment are likely to have been tested in very few individuals. Furthermore, the mechanisms for detecting new safety signals with extensively used drugs (like spontaneous reporting systems) may be much less effective with

drugs with low usage. A different, more proactive, approach is needed to conduct pharmacovigilance for low usage (including orphan) products, for example use of disease databases and active surveillance. Specialist networks and paediatric clinical trial networks may also be useful in this context.

Where unlicensed and ‘off-label’ paediatric use is common, it is the responsibility of both the marketing authorisation holder and the regulatory authorities to take appropriate measures to address any consequential safety concerns.

4 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 and the media. Depending on their responsibility the stakeholders have an important role contributing information in this process and to ensure that paediatric pharmacovigilance is effective, assessed and, through responsibly communicated risk reduction strategies, results in the safest use of products in the paediatric population, irrespective of authorisation status.

5 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. Chronic conditions may require chronic treatment and the susceptibility to adverse drug reactions (ADRs) may change throughout the patient’s life-time according to age and the stage of growth and development. Irrespective of the duration of treatment, growth and development during childhood reflect many underlying processes which may result in ADRs not seen in the adult population. Also, the associated rapid changes in body mass present additional challenges in identifying and selecting the optimal dosing regimen.

Particular problems associated with the lack of reliable data in paediatric populations include:

- lack of clinical trials in the paediatric population limits the safety data available;
- lack of kinetics data or dose-finding studies may lead to under or over-dosing in some age groups
 - under-dosing may result in lack of benefit or development of resistance
 - over-dosing may result in an increase of Type A reactions
- lack of appropriate formulations may lead to incorrect dosing, use of products of less controlled quality or inappropriately high local concentrations leading to local adverse reactions;
- routinely available safety data may not adequately capture events arising in the paediatric population.

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. 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 adverse drug reactions (ADRs) or have different drug interaction profiles;
- the paediatric population may be more susceptible to ADRs from specific excipients;
- different adverse events may be relevant for different paediatric age groups and specific pharmacovigilance tailored accordingly. In utero exposure may represent an additional risk factor;
- due to maturation, growth and development 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 ie permanent effects may result from a drug exposure at a sensitive point in development (‘critical window’), often in foetal or neonatal life;

- certain ADRs may only be seen in the paediatric population, irrespective of effects on growth and development.

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 occurs in relation to unlicensed or ‘off-label’ use.

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

6 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 than common reactions. Serious adverse events 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 some medicines it will be impossible to properly 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. Given these limitations every opportunity should be taken to maximise the information obtained from the occurrence of an ADR. For example, should an ADR occur a blood sample should be taken, if possible, and frozen for drug and metabolite measurement.

The pharmacovigilance assessment should highlight areas where data are lacking (ie 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. 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.

Whenever a medicinal product is likely to be used in the paediatric population, specific paediatric issues should be addressed in the EU Risk Management Plan (EU-RMP) that should form part of the application for marketing authorisation. A paediatric plan should be included in the Pharmacovigilance Plan (PP) and, where appropriate, specific paediatric risk minimisation activities should be included in a risk minimisation plan. The paediatric plan 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.

If not already submitted, 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.

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

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.

7.1 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 adverse drug reactions (ADRs) 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. There is also the added step of parents/carers between an event and a report of a suspected ADR reaching 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.

Unless the reluctance to report can be overcome, spontaneous reporting is expected to be of 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, poison centres, learned societies and patients/parents/carers. In order for this to have a useful impact, the regulatory authorities need to emphasise the importance of reporting to prospective reporters through targeted, structured campaigns. These should include information on what to report and how. The quality of information in the reports is particularly important in order to assess the effect of dose. Accurate information on precise age (corrected if preterm) in 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 events to health professionals. Reporting

should be simplified (eg electronic as well as paper) and made target user friendly. In this context, use of a specific form for paediatric reporting should be considered.

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

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

Medication errors are an important cause of paediatric adverse events. 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. The reporter should indicate when an adverse event occurs as a result of a medication error.

Targeted Active Data Collection

Consideration should be given to active surveillance units in view of the particular problem of under-reporting of spontaneous paediatric data. These may be based within professional bodies, learned societies, institutions or networks including regional pharmacovigilance centres, poison control centres and paediatric clinical trial networks and may target professional groups such as paediatricians (hospital-, university- or community-based), paediatric pharmacists or medicines information centers. They may make use of disease or treatment registries or national databases. 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. Although early reports are encouraging, the overall effectiveness and contribution to paediatric pharmacovigilance of targeted active data collection has still to be established.

Periodic Safety Update Reports (PSUR)

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 Note for Guidance on Clinical Safety Data Management: Periodic Safety Update Reports For Marketed Drugs [CPMP/ICH/288/95].

If there is a paediatric indication, if there is evidence of significant ‘off-label’ use or if there are adverse events reported in the paediatric population, then the use in the paediatric population should be considered 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 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 marketing authorisation should trigger a re-setting of the PSUR reporting cycle. The six monthly PSURs should focus on paediatric use.

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-analyses 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 studies¹ 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. Decisions should be made on a case by case and based on knowledge of the limitations of pre-approval database and the known or potential risks. The annex to the ICH Note for Guidance gives 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.

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 needs to be taken over the data quality review processes, including definitions of critical events and their timing. Users should also try to estimate the degree of underreporting or 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 events 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.

7.2 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 given in days or months for infants and toddlers. 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. In a short time span this

¹ Non-interventional study: a study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicines is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring process shall be applied to the patients and epidemiological methods shall be used for the analysis of the collected data.

EudraVigilance system will expand to cover all drugs authorised in the EU and will enhance the value of spontaneous reporting of adverse drug reactions. Through the data analysis tools in EudraVigilance it would be possible to run regular customised queries to detect paediatric ADRs (for instance those related to growth, development, sexual maturation).

7.3 Signal Detection

A drug safety signal may come 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 systems and processes should be in place so that they can be addressed.

For the most part, signal detection and data mining in the paediatric population depends on the detection methods used being effective for small populations and low numbers of possible cases. It is also of great importance in the calculations used for statistical signal detection tools such as proportional reporting ratios (PRRs)².

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.

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.

7.4 Risk Evaluation and Benefit Risk Assessment

As stressed in the CIOMS IV Working Group Guideline 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.

7.5 Regulatory Action

The regulatory and risk reduction tools that are available for medicines authorised for use in adults may 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.

² Evans SJ, Waller PC, Davis S Pharmacoevidenciol Drug Saf. 2001 Oct-Nov;10(6):483-6

'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 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, 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.

7.6 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 not) of data. The aim is to provide clear, unambiguous, non-alarmist information which enables risk-minimisation and informs decision-making. It should be made clear 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 relevant 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 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. 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 2004/27/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 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.

7.7 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.