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3 Guideline on good pharmacovigilance practices (GVP)

4 Product- or Population-Specific Considerations IV: Paediatric population

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Comments should be provided using this template. The completed comments form should be sent to gvp@ema.europa.eu

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P.IV.A. Introduction

The paediatric population is defined in the European Union (EU) as that part of the population aged between birth and 18 years. The paediatric population encompasses several subsets. The applied age classification of paediatric patients is:

- pre-term and term neonates from 0 to 27 days;
- infants (or toddlers) from 1 month to 23 months;
- children from 2 years to 11 years; and
- adolescents from 12 to less than 18 years[1].

Adverse reactions in the paediatric population need a specific evaluation, as they may substantially differ - in terms of frequency, nature, severity and presentation - from those occurring in the adult population (see P.IV.A.1.). The importance of performing specific research in pharmacovigilance targeting the paediatric population[2] has been recognised and established, and modalities of data collection should take into account that medicines in the paediatric population have a different utilisation pattern and often are used off-label.

Regulation (EC) No 1901/2006[3], referred to as the 'Paediatric Regulation', had put particular emphasis on the collection of safety data in the paediatric population, including data on possible long-term effects. Also, as mandated by this regulation, the European Medicines Agency (the 'Agency') issued the Guideline on the Conduct of Pharmacovigilance for Medicines Used in the Paediatric population (EMEA/CHMP/PhVWP/235910/2005), which came into effect in 2007 with the implementation of the Paediatric Regulation.

More recently, a number of changes in the scientific and regulatory environment have had direct consequences for the conduct of pharmacovigilance in the paediatric population.

Since the Paediatric Regulation came into force in 2007, the development of new paediatric medicines, and the paediatric development of medicines that were already marketed, have both increased. This is reflected by a growing number of paediatric indications for innovative medicines, newly authorised paediatric age-specific formulations, and paediatric indications for medicines with an existing marketing authorisation[4] for adults.

New pharmacovigilance legislation (Regulation (EU) No 1235/2010 and Directive 2010/84/EU) came into force in the EU in July 2012, providing for strengthened pharmacovigilance processes for all medicines, irrespective of their authorised indication(s) and population(s). This new legislation introduced changes that are particularly relevant for the paediatric population, in particular the extended definition of adverse reaction - to include harm resulting from overdose, misuse, abuse and medication errors (see GVP Annex I) - and the related broadening of the scope of pharmacovigilance to

[1] European Commission; Communication From The Commission-Guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies (2014/C 338/01): http://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/2014_c338_01/2014_c338_01_en.pdf.

[2] Impicciatore P, Choonara I, Clarkson A, et al. Incidence of adverse drug reactions in paediatric in/out-patients: a systematic review and meta-analysis of prospective studies. Br J Clin Pharmacol. 2001; 52: 77-83

[3] Regulation (EC) No 1901/2006 of the European Parliament and of the Council on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC and Regulation (EC) No 726/2004: http://ec.europa.eu/health/files/eudralex/vol-1/reg_2006_1901/reg_2006_1901_en.pdf.

[4] Report from the Commission to the European Parliament and the Council: Better Medicines for Children - From Concept to Reality General Report on experience acquired as a result of the application of Regulation (EC) No 1901/2006 on medicinal products for paediatric use (COM/2013/0443): http://ec.europa.eu/health/files/paediatrics/2013_com443/paediatric_report-com(2013)443_en.pdf.

include evaluation of risks associated with medicines when used outside the terms of the MA including 'off-label-use'.

Subsequent to the changes in the scientific and regulatory environment, the 'Guideline on the Conduct of Pharmacovigilance for Medicines Used by the Paediatric Population' (EMEA/CHMP/PhVWP/235910/2005 - rev.1) needed to be updated and the revised guidance is now provided in this Product-Specific Considerations Chapter P.IV of GVP. This guidance should therefore be read in conjunction with Title IV of the Paediatric Regulation and its Article 34, Regulation (EC) No 726/2004 and Directive 2001/83/EC.

Taking into account that the general guidance on pharmacovigilance processes in the EU is provided in GVP Modules I to XVI , the creation of this guidance as a GVP Chapter aims at integrating paediatric pharmacovigilance with the structures and processes for pharmacovigilance overall.
P.IV therefore applies in conjunction with the GVP Modules I to XVI.

In addition, the guidance in ICH E11 Guideline on Clinical Investigation of Medicinal Products in the Paediatric Population[5] applies.

The guidance contained in this Chapter is addressed to marketing authorisation applicants and holders, the competent authorities in Member States and the Agency. It covers all paediatric age groups and should additionally be of interest both to parents/carers, healthcare professionals, patient/consumer organisations and organisations of national healthcare systems in Member States.

The paediatric use of vaccines and safety surveillance of paediatric outcomes after exposure to medicines in utero are outside the scope, as such guidance is/will be provided in GVP P.I on vaccines for prophylaxis against infectious diseases and GVP P.III on pregnancy and breastfeeding.

P.IV.A.1. Pharmacovigilance aspects specific to the paediatric population

P.IV.A.1.1. Susceptibility to adverse reactions

Paediatric subjects differ substantially from adults due to the ongoing neurobehavioural development and physical growth, including internal organ maturation. Furthermore, within the paediatric population, different maturation milestones are likely to alter the susceptibility of paediatric sub-population to specific adverse reactions and the way individuals react to them (e.g. (pre)term neonates to toddlers or pre-/post-pubertal children). This is based on distinct pharmacokinetic and pharmacodynamic characteristics in the respective paediatric age groups.

Various factors might influence the susceptibility of the paediatric population to adverse reactions for a given medicine, compared to the adult population. They include:

- changes in the maturation of organ systems (e.g. skin, airways, kidney, liver, gastro-intestinal, brain and blood-brain-barrier as well as drug transporters) during growth and their development (ontogeny) leading to a different pharmacodynamic and pharmacokinetic profile of a medicine as known in adults;
- rapid changes in body mass and morphology that can reduce the therapeutic window, leading to increased susceptibility to dose-related adverse reactions;
- immaturity of many organ systems that might lead to different vulnerability to adverse reactions in some paediatric subpopulations, such as preterm neonates;

[5] http://www.ema.europa.eu

- presence of specific pharmacologically active excipients[6] that in the paediatric population may have unintended effects, leading to a risk of adverse reactions;
- impact of short and long-term effects on the developing organs and organ-systems, e.g. on neurological, skeletal growth and sexual maturation (such effects may only become obvious, visible or identifiable in the long–term, i.e. with remarkable delay, in adolescence or adulthood).

These considerations highlight the importance of taking into account aspects related to organ maturation and developmental pharmacology[7] when performing pharmacovigilance activities for the paediatric population and imply that the value of long-term follow-up should be considered systematically.

P.IV.A.1.2. Limited numbers of subjects in paediatric clinical trials

The well-known limitations of clinical trials in the generation of data on the safety profile of a medicine are even more pertinent for the paediatric population. Due to the challenges of conducting clinical trials in the paediatric population, the amount of dedicated information on the safety of medicines in neonates, children and adolescents at the time of marketing authorisation can be very limited.

The small numbers of paediatric patients that is possible to enrol in paediatric clinical trials often does not allow for a statistically-powered design for demonstration of efficacy. This has also an impact on the potential of clinical trials to gather sufficient numbers for generating dedicated information on incidence of adverse reactions in the same fashion of adult clinical trials.
Due to low numbers of patients enrolled in paediatric clinical trials and/or to the long latency between exposure to the medicinal product and the onset of the reaction, adverse reactions occurring at a frequency of less than common may not be detectable during the pre-authorisation phase.

Furthermore, the size of the paediatric safety database available for a given medicine, in comparison to what is available for adults, can be scarce or a paediatric safety database may not even be available.

P.IV.A.1.3. Medication errors

A medication error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient (see GVP Annex I). Medication errors can occur at the time of prescribing, dispensing, storing, preparing and administering a medicine. In comparison to the adult population, the impact of medication errors on the paediatric population can be much more serious. Paediatric patients are up to three times more likely to experience potential adverse reactions due to medication errors than adults[8,9]. Adverse reactions deriving from medication errors may be preventable and it is possible to enact a series of error reduction strategies[10].

Historically there has been a lack of development of medicines for paediatric patients and of paediatric dosing guidance in the product information, leading to medication errors. The Pharmacovigilance Risk Assessment Committee (PRAC) Good Practice Guide on Medication Errors[11] provides guidance on the

[6] Guideline on pharmaceutical development of medicines for paediatric use (EMA/CHMP/QWP/805880/2012 Rev. 2): http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/07/WC500147002.pdf.
[7] Tayman C., Rayyan M., Allegaert K. Neonatal pharmacology: extensive interindividual variability despite limited size. J Pediatr Pharmacol Ther. 2011; 16(3):170-184.
[8] Kaufmann J. et al. Medication Errors in Pediatric Emergencies: a systematic analysis. Deutsches Ärzteblatt International. 2012;109(38):609-616. doi:10.3238/arztebl.2012.0609.
[9] Kaushal R. et al. Medication errors and adverse drug events in pediatric inpatients. JAMA. 2001;285(16):2114-2120.
[10] Marlene R Miller, Karen A Robinson, Lisa H Lubomski, Michael L Rinke, Peter J Pronovost. Medication errors in paediatric care: a systematic review of epidemiology and an evaluation of evidence supporting reduction strategy recommendations Qual Saf Health Care 2007;16:116–126. doi: 10.1136/qshc.2006.019950
[11] www.ema.europa.eu

systematic assessment and prevention of medication errors throughout the product life-cycle, with additional considerations in paediatric patients.

P.IV.A.1.4. Off-label use

Off-label use relates to situations where a medicinal product is intentionally used for a medical purpose not in accordance with the terms of the marketing authorisation, and this includes use in non-authorised paediatric age categories (see GVP Annex I).

Off-label use of medicines that did not have an authorised indication in paediatric patients had been a widespread practice, due to the fact that necessary therapy could not be withheld from the paediatric population. This overall exposes paediatric patients to a potentially increased risk to develop adverse reactions, due to the lack of knowledge on the medicine's safety profile in this population.

With the developments described in P.IV.A., the situation nowadays has improved, but there are still a number of paediatric conditions where the need of specific paediatric medicines is not met. Furthermore, due to the limited availability of medicines with an authorised paediatric indication or an age-appropriate formulation, paediatric patients are likely to be treated with inappropriate formulations or dosages that are inferred from adult patients solely based on weight. This can expose patients to over- or underdosing which, in turn, may lead to an increased risk of adverse reactions and a lack of therapeutic effect. This risk is further increased in more vulnerable paediatric groups such as neonates.

In addition, even medicines that have an authorised paediatric indication can be used off-label when they are prescribed in non-authorised paediatric age groups.

P.IV.A.1.5. Clinical presentation of adverse reactions

The clinical presentation of adverse reactions in neonates and children may be different from adults. Most symptoms that are dependent on patient communication (e.g. nausea, pain, hallucinations) were under-represented in younger or mentally disabled children[12] in a large single centre study. In addition, some of the most common adverse drug reaction types observed in inpatients/outpatients infants and toddlers, such as vomiting and diarrhoea as well as dizziness or crying are non-specific and might be ascribed to an underlying illness in the first place. This may mean that these events are less likely to be assessed as adverse reactions.

P.IV.B. Structures and processes

P.IV.B.1. Risk management plan

The current requirements for risk management plan (RMP) (see also EMA Guidance on Format of the Risk Management Plan in the EU) in GVP Module V include considerations applicable to the paediatric population.

In general, the knowledge gained from the adult population – when available - should inform best use of data collection methods and risk minimisation tools when approaching risk management for paediatric subjects[13]. The limitation of methods used to minimise risk of adverse reactions in the adult population need to be appraised and some approaches should be subject to adaptation to target paediatric patients more effectively.

[12] Smyth RMD, Gargon E, Kirkham J, Cresswell L, Golder S, Smyth R, et al. Adverse drug reactions in children: a systematic review. PLOS ONE. 2012;7:e24061,19.
[13] Hartford CG1, Petchel KS, Mickail H, Perez-Gutthann S, McHale M, Grana JM, Marquez P. Pharmacovigilance during the pre-approval phases: an evolving pharmaceutical industry model in response to ICH E2E, CIOMS VI, FDA and EMEA/CHMP risk-management guidelines. Drug Saf. 2006;29(8):657-673.

However, there might be no previous experience in adults to build upon when a medicine is authorised for adults and paediatric patients at the same time, or it is licensed exclusively for paediatric patients, since use in real world has not yet taken place.

For medicinal products with a paediatric indication, a number of safety topics are of particular interest for the risk identification discussion in the RMP and they should be discussed if they lead to possible specific risks. Particularly important aspects for paediatric subjects are:

- age-related shifts in the interaction of the medicinal product and its target organs or tissues (including taking into account development and maturation of tissues like in the gastro-intestinal tract);
- ontogeny of the absorption, distribution, metabolism and excretion (ADME) of the medicine, including intra-individual structures such as the blood-brain barrier;
- age-related shifts in metabolic pathways related to ontogeny of ADME;
- potential adverse effects due to different exposure to metabolites as opposed to the adult age.

Evaluation of these aspects can help in assessing whether a risk of adverse reactions for a given medicine might differ from the adult population and whether its pharmacological properties justify any possibility of developmental risk.

Results of juvenile animal toxicology studies, based on the current understanding of their predictive value in terms of subsequent effects in the paediatric population[14], can also provide a useful support in prioritising pharmacovigilance research questions.

If a specific paediatric risk is highlighted and included as a safety concern in the safety specification of the RMP, consideration should be given as to whether a paediatric post-authorisation safety study (PASS) (see P.IV.B.4.) would be an appropriate tool to further characterise this risk. The conduct of a PASS in the paediatric population, or to include paediatric subjects in the population studied in a PASS, may be of particular value when:

- the medicine is authorised for both the adult and paediatric population at the same time, to evaluate risks when safety information is more limited in the paediatric population or in one of its subsets;
- it is anticipated that effects on development can only manifest years after medicine exposure;
- the paediatric clinical development and the application for a paediatric indication[15], relies heavily on extrapolation of adult or paediatric sub-group efficacy data.

P.IV.B.2. Management and reporting of adverse reactions

Spontaneous reporting of adverse reactions collected during the post-authorisation phase may be the only available primary source of information on adverse reactions occurring in the paediatric population and therefore remains, together with signal detection (see P.IV.B.2.) the most important pharmacovigilance tool so far.

[25] ICH Topic M 3 (R2) Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals. (CPMP/ICH/286/95): http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002941.pdf.
[26] International Conference on Harmonisation ICH Topic S 5 (R2). Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility. (CPMP/ICH/386/95): http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002809.pdf.
[15] EMA/199678/2016 Reflection Paper on Extrapolation of Efficacy and Safety in Paediatric Medicine Development. http://www.ema.europa.eu

The legal requirements and general guidance for the management and reporting of adverse reactions to be followed are described in GVP Module VI.

Currently, the reporting requirements of individual case safety reports (ICSRs) for the paediatric population, including those related to the off-label use, are not different from adults.
The generation of knowledge of adverse reactions reported in the framework of off-label use in the paediatric population is extremely important and could potentially serve as a substantial part of adverse reactions collected in the paediatric population.
Reporting systems should take this aspect into account to support generation of hypothesis on whether off-label use can be an independent risk factor in developing adverse reactions.

GVP Module VI includes guidance on how to collect and assess information on off-label use and potential or actual harm and enables the collection of important information on the safety of medicines in the paediatric population, where medicines are often used off-label.

However, those managing ICSRs and assessing risks of medicine use in paediatric patients should have appropriate skills to address the aspects specific to this population (see P.IV.A.1.), including to identify and obtain specific information needed for adequate signal identification, case review and risk assessment.

P.IV.B.2.1. Age information

Information on the patient's age in ICSRs should be recorded as accurately as possible (e.g. gestational age for pre-term neonates, in completed days for neonates, days or months for infants and toddlers, and completed years or months for children and adolescents).

Useful data retrieval and analysis can only be performed if age information is reported and available, and this information should be available in the structured data fields of the ICSR (rather than in the narrative).

As far as possible, the ICSRs should indicate either:

- the age at time of onset of reaction or the date of birth; or
- affiliation to one of the five paediatric age groups (see P.IV.A.) if it is not possible to obtain the exact age or date of birth or if personal data protection legislation prevent this in order to identify the patient, in particular when the medical condition is rare.

If no age-related information is provided by the initial reporter, the competent authority and the marketing authorisation holder should take follow-up action as appropriate, in order to obtain age-related data.

Additionally, information on major developmental parameters like prematurity, pubertal development stage should be collected and reported, as applicable. In this context, information on maternal and paternal exposure during conception and on pregnancy may also be of relevance since they can constitute independent risk factors for the development of adverse reactions.

For neonates and infants, the gestational age of the child at birth should also be recorded. Maturation at that time of life is rapidly evolving and cellular metabolism, receptor expression, receptor activity, enzymatic activity interrelate strongly with growth. Therefore, precise information can reveal factors leading to a different pattern in susceptibility to an adverse reaction.

P.IV.B.2.2. Other specifically relevant information

Paediatric ICSRs should also include high quality data on:

- indication or intention of use;
- formulation and dosage form;
- dose (including individual and total daily dose), duration and circumstances of exposure, including information needed to establish whether the adverse reaction has developed in a framework of medication errors or off-label use;
- weight and height, as these can vary considerably across an age group and influence the susceptibility to an adverse reaction.

The ICSRs should be as complete as possible regarding the concerned data fields and be subject to follow-up requests if these were missing, as appropriate. The robustness of the output and conclusion of the signal validation and assessment (see P.IV.B.2.) is directly related to the quality of the information included in the ICSR.

In the case of products of low usage in the paediatric population, signal detection systems could prove less effective. A different, more proactive approach may be needed to conduct pharmacovigilance for low usage products, for example using real-life data from patients' records or disease databases and active surveillance systems. Clinical specialist networks and paediatric clinical trial networks may also be a useful resource to be consulted in this context such as those being part of the European network of paediatric research at the European Medicines Agency (Enpr-EMA).

P.IV.B.3. Periodic safety update reports

The requirements for periodic safety update reports (PSUR) included GVP Module VII should be followed.

When a paediatric indication has been authorised, ongoing monitoring of the risk-benefit balance specifically for this indication throughout the product life-cycle via the PSUR should be performed, as PSURs are an important tool to collect and cumulatively analyse information on paediatric use. PSURs should explicitly address any new safety issue identified in the paediatric population overall as well as in age groups and by indication.

Assessing and discussing the use of medicines and their effects in real life is the purpose of the PSUR, which should include the paediatric population specifically (unless exempted from PSUR submission). This should be done not only when a medicine has a paediatric indication but also when:

- there is evidence of substantial paediatric use in the absence of a paediatric indication (or on the use of not age appropriate formulation) and there are critical gaps in knowledge for specific safety issues; or
- paediatric adverse reactions have been previously reported.

Furthermore, information on:

- the number of paediatric patients exposed during the reporting period and the method of exposure calculation; and
- significant findings arising from paediatric clinical trials;

should be included in the PSUR.

The addition of a paediatric indication to an existing marketing authorisation means that the population using the medicine will be widened. In some cases it would be beneficial to gather further insight on such widened use and this may lead to a requirement for a higher frequency of PSUR submissions,

which has to be considered and agreed at the time of the granting of the extension of the paediatric indication.

P.IV.B.4. Post-authorisation safety studies (PASS)

The requirements for the design and conduct of post-authorisation safety studies (PASS) in GVP Module VIII should be followed.

For the paediatric population, PASS are important complements to the research already conducted as part of pre-authorisation development[16], as they can fill potential gaps in the knowledge of the safety profile of the medicine and complement other activities such as signal detection performed on spontaneous reports. Some types of PASS such as drug utilisation studies may be useful in describing how the medicine is used in the paediatric populations in real-life clinical practice, e.g. how frequently and which paediatric groups are treated. Furthermore, PASSs are important to understand the effectiveness of risk minimisation measures.

The design and conduct of PASS in the paediatric population should take into account the specific characteristics of the paediatric (sub-)population under investigation (P.IV.A.1.), that may lead in confounding due to factors relating to child development, imprecise diagnostic coding and medical record limitations, as well as lack of consensus about best research standard for paediatrics in some areas. Challenges arising from specific ethical and feasibility aspects could compromise PASSs conduction. Therefore such aspects should also be addressed in a PASS protocol demonstrating that they will be appropriately managed.

Disease or treatment registries and national healthcare databases can be used for the conduct of non-interventional PASS, but because of the inclusion of paediatric patients in these types of data sources can be limited, multi-database approaches should be considered to achieve appropriate study sizes.

In many cases high level planning for such studies should already be considered at the time of submission of a Paediatric Investigation Plan (PIP, see P.IV.B.6.2.3), to promote continuity between the safety data generation in the pre- and post-marketing phase. An early planned study would facilitate understanding on possible types of data that can be gathered after marketing authorisation and can support in defining main characteristics and requirements for paediatric registries that can be set-up more promptly, enabling to address research questions arisen in the pre-marketing phase.

The template for PASS protocols (see GVP Module VIII, Guidance for the Format and Content of the Protocol of Non-Interventional Post-Authorisation Safety Studies[17]) should be completed, taking into account specifics for paediatrics as follows:

- template heading 8 "Research question and objectives": this may relate to alterations in somatic growth, puberty, cognitive or physical development;
- template heading 9.4 "Data sources": if information from other family members or from external data sources, such as census data, is needed, the linkages to external data sources and the sources should be described (e.g. exposures and events in neonates are often included in the mother's clinical record rather than in a separate record for the child);
- template heading 9.7 "Data analysis": the statistical methods may need to be adapted to account for paediatric-specific aspects (e.g. the correlation between repeated measurements such as

[16] Andrews EB, Moore N, eds. Mann's Pharmacovigilance. 3rd ed. Wiley-Blackwell.; 2014.
[17] www.ema.europa.eu

weight and height)in the same child which may vary in short periods of time; changes in recommended dosing as the child grows).

P.IV.B.5. Signal management

A signal is information arising from one or multiple sources, including observations and experiments, suggesting a new potentially causal association, or a new aspect of a known association between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action (see GVP Annex I). Guidance for signal management as provided in GVP Module IX should be followed.

Signal management activities focussing on the paediatric population should take into account the expected differences in this age group compared to adults, as previously discussed, due to the different utilisation, prescription, adverse reaction susceptibility and clinical presentation.

Further, it has been shown that the types of medicines and the suspected adverse reactions commonly reported in spontaneous reports, differ substantially between paediatric patients and adults, not only in terms of reaction types and medicinal products involved, but also in the fact that they are more concentrated around limited sets of reaction types and medicinal product type, such as vaccines[18]. Hence, performing paediatric statistical signal detection may benefit from tailored approaches as well as specific tools to study a heterogeneous population, weighing whether age group may be a confounder or an effect modifier.

Such tailored approaches aim firstly at addressing whether an adverse reaction is new or more severe than previously known, in one or all paediatric age groups.

Qualitative differences in usage of medicines and reporting of adverse reactions have suggested that paediatric ICSRs should be analysed separately from ICSRs about adult patients in the systems like the electronic Reaction Monitoring Reports (eRMRs) produced by EudraVigilance[19].

Another approach to enhance signal detection in the paediatric population may be targeting reported medical events that are particularly relevant in this population, i.e. adverse reactions that are more frequently associated with a fatal or more serious outcome when they occur in paediatric patients as compared to adults.

As for the general population, statistics of disproportionate reporting (see GVP Module IX Addendum I) should be calculated using only ICSRs about paediatric patients to increase the ability to detect paediatric signals of disproportionate reporting (SDR) from spontaneous databases. Sub-group analysis by age and comparison of the disproportionality statistics in paediatric patients versus adults can help to determine whether or not a suspected adverse reaction is likely to be more frequent in paediatric patients.

Additionally, the signalling threshold based on the number of ICSRs received, should be lower than that for the whole population. As the number of cases is usually small, there needs to be a high index of suspicion, comprehensive assessment of individual cases, and a follow-up strategy should be in place to consistently complete ICSRs with essential information.

Since some adverse reactions might be age-specific, a stratification of the ICSR analysis by age sub-

[18] Blake KV, Zaccaria C, Domergue F, La Mache E, Saint-Raymond A, Hidalgo-Simon A. Comparison between paediatric and adult suspected adverse drug reactions reported to the European medicines agency: implications for pharmacovigilance. Paediatr Drugs. 2014;16(4):309-319.
[19] Screening for adverse reactions in EudraVigilance; http://www.ema.europa.eu.

groups can be essential to yield additional evidence to gain understanding of the risk and/or the risk groups.

Considering that the nature and/or severity of adverse reactions in paediatric patients may depend on organ maturation stage, any signal detection methods should focus not only on the paediatric population as a whole, but also on specific paediatric subpopulations.

In case of medicinal products with low usage in the paediatric population, early signal detection can prove more challenging. A different, more effective approach may be needed, for example using real-life data from patients' records or disease databases and active surveillance systems. Clinical specialist networks and paediatric clinical trial networks may be a useful resource in this context.

P.IV.B.6. Safety communication

For safety communication about paediatric medicines, the general guidance in GVP Module XV on safety communication and GVP Module XVI on risk minimisation measures (RMM) should be followed, together with the considerations in this Section.

It should be considered that children and adolescents are becoming increasingly involved in medical decision-making process and, as they are reaching adulthood, they want to be involved in making their own health choices. With the increasing use of the internet, young people tend to independently seek health information. Children above 12 years of age usually take their chronic medicine independently, and even younger children may learn to do so. Adolescents can and want to be informed about medicines in a way similar to adults, while younger children can be approached with information in an adapted style that takes into account their information and capability of processing complex messages avoiding a paternalistic style.

Safety communication and communication-based RMM should include targeting specific audiences, (e.g. paediatricians, parents/carers or legal representatives, and the paediatric population, as relevant), and aim at gaining their active participation in risk minimisation and informed therapeutic choice, involving the child as appropriate to their age.

In order to convey information specifically of interest to the paediatric population, marketing authorisation holders and competent authorities are encouraged to address the following if evidence is available:

- interference of the effects of the medicinal product with school and sports performance;
- interactions with alcohol, nicotine and other pharmacologically active substances;
- risks of diversion of the medicine to friends.

Younger people have different media preferences and may be more effectively reached by information and educational tools like infographics, comics, video clips and social media channels. This should be considered in the preparation of additional RMM.

In some situations, educational materials for additional RMM targeted to parents/carers should be considered, e.g. when advice on correct administration of a medicine is particularly important or to alert on a risk of diversion and/or misuse.

Safety communication and, when necessary, educational materials addressed to healthcare professionals should aid discussion on certain risks with children and their parents/carers or legal representatives. Where applicable, the advice needs to address common sensitivities and concerns, such as the impact of the medicinal product on growth and development, cognitive and sexual/reproductive functions, and potential long-term effects.

P.IV.C. Operation of the EU network

P.IV.C.1. Roles and responsibilities

P.IV.C.1.1. Marketing authorisation holder and applicant in the EU

The marketing authorisation holder or applicant in the EU has the legal obligation to conduct pharmacovigilance in accordance with the requirements set up in Directive 2001/83/EC and Regulation EC no 726/2004 and should address the specific aspects relevant to the paediatric population (see P.IV.A.1.) in accordance with the guidance provided in P.IV.B.. The guidance in P.IV.C.1., should be followed for addressing paediatric-specific aspects when operating in the EU.

P.IV.B.6.1.1. Risk management plan (RMP)

Further to the guidance in P.IV.B.1., the following should be considered:

When agreeing a paediatric investigation plan (PIP) (see P.IV.C.2.3.), the Paediatric Committee (PDCO) (see P.IV.C.2.1.) may identify, in the PDCO opinion, potential risks for the paediatric (sub-) population(s), in particular with regard to long-term efficacy and/or safety. PRAC will consider at the moment of the marketing authorisation in a paediatric indication whether the available clinical and non-clinical evidence supports their inclusion as important potential or identified risks, or missing information in the RMP.

The PDCO might also waive the requirement of paediatric development (Article 11 of the Paediatric Regulation) on the grounds that the specific medicinal product is likely to be ineffective or unsafe of the paediatric population [Article 11(1)(a) of the Paediatric Regulation]. Once the clinical programme has been completed in adults the applicability of such grounds will be confirmed by PRAC and CHMP at the time of MA for potential inclusion of adequate information on paediatric subjects in the summary of product characteristics (SmPC) as well as in the RMP. This aims at setting-up appropriate risk minimisation measures should there be a potential paediatric use.

P.IV.B.6.1.2. Periodic safety update report (PSUR)

Further to the guidance in P.IV.B.3., the following should be considered:

Significant findings arising from paediatric clinical trials during the PSUR reporting period should be included in the PSUR, especially when these clinical trials have included safety objectives as part of the agreed PIP opinion which is not yet completed, facilitating cross-linking of information and procedures in the management of the medicinal product life-cycle.

When the PSUR submission is due before the paediatric development is completed, as agreed in a PIP, all information related to the deferred clinical and non-clinical studies should be adequately presented.

Where it is considered beneficial to gather further insight on widened use of a medicine in the paediatric population, this may lead to a requirement for a higher frequency of PSUR submissions as required by means in the List of European Union Reference Dates[20] (see GVP Module VII).

P.IV.B.6.1.3. Post-authorisation safety study (PASS)

Further to the guidance in P.IV.B.4., the following should be considered:

[20] www.ema.europa.eu

In the case of development of medicines to treat diseases which occur rarely in paediatric patients and for which paediatric data are lacking or very limited, long term follow-up and maintenance of registries to document the long term outcome should be considered by the marketing authorisation holder(MAH).

Finally, the clinical study program to be conducted in the paediatric population following initial marketing authorisation (MA) in adults (deferred paediatric clinical studies as described in the PIP opinion) should be reviewed at time of initial marketing authorisation application. This is important because specific safety objectives included in the agreed clinical trial can consequently be considered for inclusion in the RMP (part II, modules SVII and SVIII).

The consultation of specialist networks (e.g. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance [ENCePP][21]) and where appropriate, paediatric clinical trial networks (e.g. Enpr-EMA[22]) could be helpful to address specific aspects related to design and conduct of PASS in paediatrics.

P.IV.B.6.2. European Medicines Agency

For the purpose of safe and effective use of medicinal products authorised for or used by the paediatric population outside the terms of the marketing authorisation the Pharmacovigilance Risk Assessment Committee (PRAC) (see GVP Module I) and the Paediatric Committee (PDCO) work together.

P.IV.B.6.2.1. The Paediatric Committee (PDCO)

The Paediatric Committee (PDCO) supports the development of such medicines in the European Union and its responsibility is to assess the content of paediatric investigation plans (PIPs), which determine the studies that must be carried out in the paediatric population when developing a medicine. This includes assessing applications for a full or partial waiver and for deferrals.

The PDCO composition includes members with expertise in pharmacovigilance to meet the specific challenges of collecting safety data in the paediatric population, including data on possible long-term effects. The Mandate and Rules of Procedure of the PDCO are published on the Agency's website[23].

P.IV.B.6.2.2. Interaction between the PDCO and the PRAC

While the regulatory role and competences of the PRAC and the PDCO remain clearly separated, a scientific dialogue and coordination in the respective procedure is expected. The PDCO and the PRAC proactively exchange of information and provide each other reciprocal advice.

The scope of such interaction focuses on the promotion of early development of risk management strategies, understanding impact of emerging safety issues on paediatric development, gaining insight on paediatric needs and ensuring in general that, when needed, pharmacovigilance mechanisms are adapted to meet the specific challenges of collecting safety data in the paediatric population.

P.IV.B.6.2.3. Paediatric investigation plan in the EU (PIP)

A PIP is a development plan aimed at ensuring that the necessary data are obtained through studies in the paediatric population, to support the authorisation of a medicine with a paediatric indication. A PIP might include for example, interventional and non-interventional studies, non-clinical studies,

[21] European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP): http://www.encepp.eu/.
[22] European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA): http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/general/general_content_000303.jsp.
[23] http://www.ema.europa.eu.

extrapolation studies, modelling and simulation studies, development of specific paediatric pharmaceutical forms and formulations.

All applications for marketing authorisation for new medicines in the EU have to include the results of studies as described in an agreed PIP, unless the medicine is exempt because of a deferral or waiver. This requirement also applies when a marketing-authorisation holder wants to add a new indication, pharmaceutical form or route of administration for a medicine that is already authorised and covered by intellectual property rights.

P.IV.C.2. Safety communication in the EU

Further to the guidance in P.IV.B.5., children and their families in the EU, through the established Young Person Advisory Groups (YPAG) can be consulted for the preparation of safety communication and educational materials for additional RMMs. To this extent it is important to emphasise the activities of the EnprEMA Working Group on Young Persons Advisory Groups which is currently working on resources for the EMA and marketing authorisation holders in the EU.