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Product- or Population-Specific Considerations IV: Paediatric population

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P.IV.A. Introduction

The paediatric population is defined in the European Union (EU) as that group of the population between birth and 18 years of age. The paediatric population encompasses several subsets. In accordance with current guidelines[1,2], the applied age classification of paediatric patients is:

- preterm newborn neonates: from day of birth through the expected date of delivery plus 27 days;
- term and post-term neonates: from day of birth plus 27 days;
- infants (or toddlers): from 1 month (28 days) to 23 months;
- children: from 2 years to 11 years; and
- adolescents: from 12 years to less than 18 years.

Adverse reactions to medicinal products in the paediatric population need 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 tailored pharmacovigilance research in the paediatric population[3] has been recognised and established. Collection of pharmacovigilance data should take into account that in the paediatric population medicines have different utilisation patterns and are often used off-label, i.e. intentionally used for a medical purpose not in accordance with the terms of the marketing authorisation.

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, referred to as the 'Paediatric Regulation', puts particular emphasis on the collection of safety data in the paediatric population, including data on possible long-term adverse effects.
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 rev 1), which came into effect in 2007 with the implementation of the Paediatric Regulation.

Since the Paediatric Regulation came into force, a number of changes in the scientific and regulatory environment have had direct consequences for the conduct of pharmacovigilance in the paediatric population, in particular the following:

- the development of new paediatric medicines - as well as 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 new paediatric indications for medicines with an existing marketing authorisation for adults[4];
- new pharmacovigilance legislation, i.e. Directive 2010/84/EU amending Directive 2001/83/EC (the latter is referenced in this guidance as DIR) and Regulation (EU) No 1235/2010 amending Regulation (EC) No 726/2004 (the latter is referenced as REG), came into force in July 2012,

[1] ICH-E11(R1) Guideline on Clinical Investigation of Medicinal Products in the Paediatric Population.
[2] 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).
[3] 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.
[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).

providing for strengthened pharmacovigilance processes for all medicines, irrespective of their authorised indication(s) and population(s).

This pharmacovigilance legislation introduced changes that are relevant for the paediatric population. In particular the extended definition of adverse reaction now acknowledges that adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure [DIR Art 101(1)]. Use outside the marketing authorisation includes off-label use, overdose, misuse, abuse and medication errors (see GVP Annex I), which are all important aspects related to the pattern of utilisation of medicines in the paediatric population (see P.IV.A.1.4.).

Consequent to these changes, the previous guideline EMEA/CHMP/PhVWP/235910/2005 rev 1 needed to be updated, and revised guidance is now provided in this Product-Specific Considerations Chapter P.IV of the Good Pharmacovigilance Practices (GVP). This guidance should 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.

The creation of this guidance as a GVP Considerations Chapter, aims at integrating paediatric pharmacovigilance within the structures and processes for pharmacovigilance overall. P.IV therefore applies in conjunction with the GVP Modules I to XVI on pharmacovigilance processes in the EU and does not replace these GVP Modules or introduce regulatory requirements in addition to those already covered in existing Modules. This Chapter provides guidance on how to make best use of the pharmacovigilance tools and processes to address the needs and specific challenges of the paediatric population, and supports the interpretation of how regulatory requirements should be adapted to target this specific population.

The guidance contained in this Chapter is addressed to marketing authorisation applicants and holders, and to the competent authorities in the Member States and the Agency. Additionally it will be of interest to parents/carers, healthcare professionals, patient/consumer organisations, healthcare professional organisations, organisations of national healthcare systems in Member States as well as sponsors of clinical studies.

This guidance is addressed primarily to cover medicines with a paediatric indication or those with an adult indication and ongoing paediatric development, but also to medicines with an adult indication for which there is evidence of use in the paediatric population.

The paediatric use of vaccines and the safety surveillance of paediatric outcomes after exposure to medicines in utero are outside the scope of P.IV., as such guidance is covered by GVP P.I and GVP P.III.

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

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

Due to growth and maturation, the susceptibility of paediatric patients to adverse reactions may substantially differ from adults. Various factors account for this difference and include, but are not limited to:

- changes in physiology during growth and development (ontogeny), that may lead to different pharmacodynamic and pharmacokinetic parameters in the paediatric subjects compared to adults having an impact on the safety profile of the medicine;
- immaturity of some organ systems (e.g. skin, airways, kidneys, liver, gastro-intestinal system, brain and blood-brain-barrier, immune system, bones, drug transporters) that may increase the vulnerability to adverse reactions and their sequelae;

- changes in body mass and composition that may lead to a narrowing of the therapeutic window and an increased susceptibility to dose-related adverse reactions;
- increased sensitivity to pharmacologically active excipients[5] that may lead to an increased risk of adverse reactions.

Within the paediatric population itself, the different maturation milestones might alter the susceptibility to specific adverse reactions across the various paediatric sub-populations (e.g. (pre)term neonates to toddlers or pre-/post-pubertal children).

Moreover, effects on developing organs and organ systems - e.g. on skeletal growth, sexual maturation, neurobehavioral development[6] - may only become obvious, visible or identifiable with significant delay after exposure or long-term use (i.e. in adolescence or adulthood).

These considerations highlight the importance of taking into account aspects related to organ maturation, developmental physiology and developmental pharmacology[7] when planning pharmacovigilance activities for the paediatric population. Considerations for long-term follow-up should carefully take these factors into account.

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

Clinical trials conducted in adults have known limitations in generating safety data. Trials often are limited in size and in duration, might exclude high-risk populations and have limited statistical power to detect rare, but potentially serious, adverse reaction that will only be detected in the real-world setting. These limitations are even more relevant for paediatric clinical trials.

Due to the small numbers of patients that is generally possible to enrol, paediatric clinical trials often have a sample size that is not statically-powered for demonstration of efficacy and cannot gather a sufficient number of participants for collecting precise information on the incidence of adverse reactions, particularly in some paediatric age sub-groups. Adverse reactions that are rarer than 'common', i.e. occur at a frequency of less than 1/100[8], may not be detectable in clinical trials. Also, the duration of such trials is usually limited, and adverse reactions that have a long latency between exposure and onset might not be adequately captured.

Overall, this means that the safety data collected for neonates, infants, children and adolescents for a given medicine in comparison to what is generally available for adults at the time of granting the marketing authorisation, can be particularly limited.

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, storing, dispensing, preparing as well as administering a medicine.

Historically, there has been limited development of medicines for paediatric patients, leading to the absence of specific paediatric dosing guidance in the product information, and scarcity of age-

[5] Guideline on pharmaceutical development of medicines for paediatric use (EMA/CHMP/QWP/805880/2012 Rev. 2), https://www.ema.europa.eu/documents/scientific-guideline/guideline-pharmaceutical-development-medicines-paediatric-use_en.pdf.
[6] Hetrick SE, McKenzie JE, Cox GR, Simmons MB, Merry SN. Newer generation antidepressants for depressive disorders in children and adolescents. Cochrane Database of Systematic Reviews. 2012 Issue 11. Art. No.: CD004851.
[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] European Commission. A guideline on summary of product characteristics (SmPC). Rev 2; 2009 (in Volume 2C of the Rules Governing Medicinal Products in the European Union).

appropriate pharmaceutical forms or presentations. Due to the limited availability of medicines with an authorised paediatric indication and/or with an age-appropriate pharmaceutical form, paediatric patients may be treated at dosages that are inferred from adult patients, solely based on weight considerations, or with inappropriate pharmaceutical forms (e.g. tablets instead of syrups or drops). Such widespread practice of off-label use (see P.IV.A.1.4.) was, and still is, associated with a risk of medication errors. Since these medication errors might lead to the administration of inappropriate doses (such as overdose or sub-therapeutic dose), paediatric patients are exposed to a higher risk of developing adverse reactions than adults[9,10].

Furthermore, the consequences of such medication errors in can also be much more serious particularly in the most vulnerable paediatric age sub-groups such as neonates.

It is expected that increased availability of new products with specific paediatric indications and age-appropriate form and presentations (see P.IV.A.1.) will reduce adverse reactions deriving from medication errors in the future.

The Pharmacovigilance Risk Assessment Committee (PRAC) Good Practice Guide on Risk Minimisation and Prevention of Medication Errors [11] provides guidance on the systematic assessment and prevention of medication errors throughout the product life-cycle and contains additional considerations applicable to paediatric patients. These include calculation tables in educational material, appropriate dispensing devices and presentations and recommendations for enhanced communication between healthcare professionals, patients and their parents/carers. Advice on appropriate prescribing, storing, dispensing, preparing and administration of medicines, as well as monitoring of patients is also provided. Such strategies and measures for risk minimisation and prevention of medication errors should be considered when developing paediatric medicines or risk management plans.

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

Off-label use indicates situations where a medicinal product is intentionally used for a medical purpose not in accordance with the terms and conditions of the marketing authorisation. Relevant cases are where the use of a medicine is indicated solely for adults, but is nonetheless used in paediatric subjects (possibly with a different dosage, different route of administration and/or to treat a specific paediatric condition) (see GVP Annex I), or when a paediatric indication exists that is limited to some paediatric age sub-groups, but the product is also used in other age sub-groups (e.g. a medicine is indicated only in adolescents but is used also in children).

Off-label use of medicines in paediatric patients has been a common practice, due to the fact that paediatric-specific medicinal products were not available, but necessary therapy could not be withheld. With the developments described in P.IV.A., the situation nowadays has improved, but there are still a number of medical conditions where the need for specific paediatric medicines is not met and off-label use continues.

Such off-label use, as discussed above, might expose paediatric patients to an increased risk of medication errors and of adverse reactions. Therefore, it is relevant that important risks arising from off-label use in paediatric patients are addressed appropriately (see P.IV.B.1.).

[9] Kaufmann J, Laschat M, Wappler F. Medication errors in pediatric emergencies: a systematic analysis. Deutsches Ärzteblatt International. 2012; 109(38): 609-616.
[10] Kaushal R, Bates DW, Landrigan C. Medication errors and adverse drug events in pediatric inpatients. JAMA. 2001; 285(16): 2114-2120.
[11] www.ema.europa.eu.

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

Signs and symptoms of adverse reactions and their clinical course may be different in paediatric patients compared to adults. This is also true among the various paediatric age sub-groups. Non-specific symptoms, such as vomiting and diarrhoea as well as sleepiness or variation in the intensity and pattern of crying, can be the only manifestations of some adverse reaction observed in neonates, infants and toddlers. Moreover, symptoms that are dependent on patient communication ability (e.g. nausea, pain, mood alterations) in younger or mentally disabled children[12] might be under- or misreported.

This means that the clinical presentation of adverse reactions can be non-specific and be misinterpreted as the manifestation of a pre-existing condition. As such these reactions will be less likely to be suspected and reported.

Aspects relating to the modalities of presentation of adverse reactions in the paediatric population (see P.IV.B.5.) need to be taken into account when choosing the most appropriate search terms for performing signal detection (e.g. Lowest Level Terms and Preferred Terms when performing Standardised MedDRA Queries (SMQs)). This is also important when planning pharmacovigilance activities that might involve an active role of the paediatrician and of parents/carers, as they should be enabled to interpret particular signs and symptoms (e.g. crying and pain).

P.IV.B. Structures and processes

P.IV.B.1. Risk management plan (RMP)

The current requirements for risk management plans (RMP) in GVP Module V and the Guidance on the format of the risk management plan (RMP) in the EU – in integrated format[13] includes considerations for the paediatric population. Methods used to minimise risk of adverse reactions in the adult population should be evaluated and adapted to paediatric patients, taking into account the aspects specific to the paediatric population (P.IV.A.1.).

In terms of pre-clinical evidence, results of juvenile animal toxicology studies can have a predictive value in terms of effects in the paediatric population and can support prioritising pharmacovigilance research questions (e.g. accumulation of active substance in some organs of the animals tested, impairment in some behavioural tests).

Regarding existing clinical data, the knowledge gained from studies in the adult population should support in the identification of important potential risks, in the characterisation of the safety profile as well as the description of tools to reduce the risk related to the use of the product[14] in the paediatric population.

Sometimes no previous clinical or real-world data from adults are existing: this might happen when a medicine is authorised exclusively for paediatric patients or when it is authorised for adult and paediatric patients at the same time.

Conversely, a paediatric indication might be added after considerable post-marketing experience has been gained in adults. Therefore, the amount of available evidence can vary greatly.

[12] Andrews EB, Moore N, eds. Mann's Pharmacovigilance. 3rd ed. Wiley-Blackwell; 2014.
[13] www.ema.europa.eu.
[14] Hartford CG, 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.

Particularly important aspects to be considered for paediatric patients for the purpose of risk identification and characterisation include:

- age-related shifts in the interaction of the medicinal product with its target organs or tissues;
- ontogeny of the absorption, distribution, metabolism and excretion (ADME), including disposition in intra-individual structures (such as the blood-brain barrier), of an active substance;
- potential adverse reactions due to different exposure to (different) metabolites as opposed to the adult age;
- long-term effect on developing reproductive and neurodevelopmental systems;
- effects on bone and cartilage during active growth phase;
- impact on maturation of the immune system in the pathogenesis of known adverse reactions and effect of transition from passive maternal immunity to maturing immune systems in infants.

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 suggest any possibility of developmental risk.

Similarly, when it is anticipated that a subgroup of the paediatric population is likely not to be different from the adult population (e.g. post-pubertal children, children above a certain age and/or weight), this should be supported by evidence and discussed at the time of the initial marketing authorisation application.

If a specific paediatric risk is highlighted and is included as a safety concern in the RMP - in line with the guidance provided in GVP Module V - consideration should be given as to whether a paediatric post-authorisation safety study (PASS) (see P.IV.B.4.) would be appropriate for further characterising this risk.

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

Spontaneous reporting is an indispensable pharmacovigilance tool, which may even be the only source of information on adverse reactions occurring in the paediatric population in the post-authorisation phase for some medicines.

Since the use of medicinal products in the paediatric population might occur off-label, data from spontaneous reports can be instrumental in discovering new, specific or more serious adverse reactions in the paediatric population in comparison to that found in the authorised population.

The legal requirements and general guidance for the management and reporting of adverse reactions to be followed, including adverse reactions resulting from off-label use, are described in GVP Module VI.

Reporting systems in place should ensure that the relevant data on paediatric cases (see P.IV.B.2.1. and P.IV.B.2.2.) are fully obtained.

Staff performing pharmacovigilance activities should have appropriate skills and training to address the aspects specific to the paediatric population (see P.IV.A.1.), including for identifying and obtaining specific information needed for adequate signal identification, review of individual case safety reports (ICSRs) and risk assessment.

Where off-label use is involved, complete ICSRs can support the generation of hypothesis on whether off-label use is more likely to be associated with an increased reporting of adverse reactions (e.g. an

association of off-label use leading to over- or under-dosing and formulation related issues). Therefore completeness of ICSRs is important.

P.IV.B.2.1. Age information

Information on the patient's age in ICSRs should be recorded as accurately as possible (i.e. 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 this information should be available in the structured data fields of the ICSR (rather than only 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, and for neonates, pre-term neonates and infants in addition the gestational age; or
- affiliation to one of the paediatric age subsets if it is not possible to obtain the exact age or date of birth or if personal data protection legislation do not permit this in order to prevent identifying the patient, in particular when the medical condition is rare.

If no age-related information is provided by the initial reporter, the marketing authorisation holder or the competent authority should request, as appropriate, follow-up information on age.

Additionally, information on major developmental parameters like prematurity, pubertal development stage or cognitive and motor developmental milestones should be collected and reported when relevant to the suspected adverse reaction, because maturation can highly vary in children and can be clinically more important than age.

Particularly in younger subjects, information on maternal and paternal exposure to medicines during conception or pregnancy as well as exposure of the neonate/infant through breastfeeding may also be of relevance since such exposure can lead to adverse reactions in the off-spring.

Additionally, information on birth history as well as major developmental parameters should be collected when possible and where relevant. Maturation at that early time of life is rapidly evolving and cellular metabolism, receptor expression, receptor activity, enzymatic activity interrelate strongly with growth. Therefore, precise information on this can reveal factors leading to a different pattern in susceptibility to an adverse reaction in term or pre-term neonates.

P.IV.B.2.2. Other information relevant to the paediatric population

Paediatric ICSRs should also include data as complete as possible on:

- indication or intention of use, including information needed to establish whether the adverse reaction has developed in association with a medication error or off-label use;
- pharmaceutical form and strength of the medicinal product;
- dosage prescribed and/or administered (including single, daily and/or total dose as well as dosing schedule), duration and circumstances of exposure, method used to determine the dosage and treatment compliance;
- weight and height/length at the time of the reaction, 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 are missing, as appropriate. It is important to capture this information, as the robustness of the output and conclusion of the scientific assessment will be directly related to the quality of the information included in the ICSRs.

P.IV.B.3. Periodic safety update report (PSUR)

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

When a paediatric indication has been granted, ongoing monitoring of the risk-benefit balance specifically for this indication throughout the product life-cycle should be performed (unless exempted from PSUR submission with a justification) via the PSURs, as they 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 (and when feasible paediatric age sub-groups) and by indication. Discussing and assessing the use of medicines and their effects in real life is the purpose of the PSUR, and this applies not only when a medicine has a paediatric indication but also when information of the safety of a medicinal product used in paediatric patients has been derived from the evaluation of other data related to:

- off-label use, including the use of not 'age-appropriate' formulations or use in paediatric sub-groups for which the product is not authorised; or
- an identified signal of a paediatric adverse reaction.

In both these situations, information on the number of paediatric patients exposed during the PSUR reporting interval, the exposure of patients by age sub-group and the method of exposure calculation should be included in the PSUR.

It is acknowledged that in some cases it is difficult to obtain and validate paediatric exposure data. Nevertheless, estimations based on available sources (see GVP Module VII), or a justification if it is not possible to draw accurate estimations, should be provided. Safety related findings arising from ongoing or completed paediatric clinical trials should also be discussed.

The addition of a paediatric indication to an existing marketing authorisation implies that the population using the medicine will be widened. It is considered beneficial to gather further insight on the benefit-risk balance in this widened population and in certain cases this may lead to a requirement for a change towards a higher frequency of PSUR submissions, which can be requested by a competent authority, on a case-by-case basis, or proposed by the marketing authorisation holder for agreement at the time of the granting of an extension of the indication.

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

For the paediatric population, post-authorisation safety studies (PASS) are important additions to the research already conducted as part of pre-authorisation development[15], as they can fill in gaps in the knowledge of the safety profile of the medicine and complement other activities such as signal detection performed on spontaneously reported adverse reactions. The conduct of a PASS in the paediatric population, or inclusion of paediatric patients in a PASS study population, may be of particular value when:

- it is anticipated that effects on development can only manifest years after medicine exposure;

[15] Andrews EB, Moore N, eds. Mann's Pharmacovigilance. 3rd ed. Wiley-Blackwell; 2014.

- the paediatric clinical development and the paediatric indication[16] relies heavily on extrapolation of adult or paediatric sub-group efficacy data (a paediatric PASS could be considered to investigate long-term safety in children which would have been identified as missing information in the RMP as applicable (see P.IV.B.1.);
- data on long-term safety are needed because of chronic use, particularly for medicines with innovative mechanism of action and/or when chronic use in younger children is expected (i.e. neonates, infants, children below 6 years);
- there is a high likelihood of off-label use in paediatric patients and a safety issue has been suspected as derived from such use (this risk should have been included as an important potential risk in the RMP (see P.IV.B.1.)).

The requirements for the design and conduct of post-authorisation safety studies (PASS) as described in GVP Module VIII should be followed. The design and conduct of PASS in the paediatric population should take into account the specific characteristics of the paediatric sub-populations (see P.IV.A.1.) which may result in effect modification due to a number factors (e.g. relating to child physical maturation and development).

There might be a lack of consensus about the best research methodological tools in relation to some aspects characteristic to the paediatric population (e.g. misclassification of exposure data, need to choose appropriate risk window, imprecise diagnostic coding and medical record limitations) and this needs to be taken into account in order to choose the most appropriate approach. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology[17] provides useful recommendations to address paediatric-related aspects of observational studies and should be taken into account.

Ethical and feasibility aspects may also compromise the implementation and conduct of PASS. Therefore, when developing of a PASS protocol, a PASS feasibility report should also be considered in order to demonstrate that these aspects will be appropriately managed (e.g. providing estimated recruitment figures based on evidence or a remedial strategy in the case that the target patient number is not reached in time) as this can support the smooth implementation of the study.

Disease or treatment registries and national healthcare databases can be used for the conduct of non-interventional PASS[18]. However, since 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.

Planning a PASS early, at the same time when the clinical development is defined, can enable a synergist approach supporting a more fruitful strategy for the integration of data to be produced prior to marketing authorisation with data that will be collected after marketing authorisation. An early planning can also help in a better definition of the main characteristics and requirements for future paediatric registries to be put in place. They could be set-up more promptly enabling researchers to address safety-related questions arisen in the pre-authorisation phase, once a product is authorised, more promptly.

[16] Reflection Paper on Extrapolation of Efficacy and Safety in Paediatric Medicine Development (EMA/199678/2016), www.ema.europa.eu.
[17] www.encepp.eu/standards_and_guidances.
[18] de Bie, S et al. The role of electronic healthcare record databases in paediatric drug safety surveillance: a retrospective cohort study. Br J Clin Pharmacol. 80: 304-314.

P.IV.B.5. Signal management

A signal is the 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 [Commission Implementing Regulation (EU) No 520/2012, Art 19(1) (hereafter referred to as IR 520/2012)].

For the purpose of monitoring data in the EudraVigilance database, only signals related to an adverse reaction shall be considered [IR 520/2012 Art 19(1)] (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 compared to adults, due to the different utilisation, prescription, adverse reaction susceptibility and clinical presentation (see P.IV.A.1.).

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

It has been shown that the more commonly reported classes of medicines and suspected adverse reactions described in spontaneously reported ICSRs, differ substantially between paediatric and adult patients; not only the reaction types and medicinal products involved are different, but they are also more concentrated around limited sets of reaction types and medicinal product types, such as e.g. vaccines[19]. Qualitative differences observed in the usage of medicines and in the reporting of adverse reactions have suggested that, when existing, paediatric ICSRs should be analysed independently from ICSRs in adult patients by competent authorities and marketing authorisation holders.

When paediatric signal detection is performed, tailored statistical approaches as well as specific tools to study a heterogeneous population should be considered aiming at identifying whether in one or all paediatric age sub-groups an adverse reaction is new, more severe or more frequent than previously known or if there are any differences in the reversibility of the reaction. Together with appropriate clinical considerations, they should also aim at investigating confounding or effect modification by specific age sub-groups.

When using statistical algorithms in signal detection, the signalling threshold based on the number of ICSRs received should be adapted to the exposure in the paediatric population as opposed to that for the whole population (for exposure calculation, see GVP Module VII). As the absolute number of cases is usually small, comprehensive assessment of ICSRs should be underpinned by a follow-up strategy consistently completing ICSRs with essential information for signal detection and assessment.

Since some adverse reactions might be age-specific, a stratification of the ICSR analysis by age sub-groups can be useful to yield additional evidence and understanding of the risk and/or risk groups. However, stratification is scientifically justified once an adequate number of cases have been reported and are well documented.

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

[19] 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.

population as a whole, but also on specific paediatric subpopulations defined by age or maturation status.

In case of medicinal products with low usage in the paediatric population, early signal detection can prove more challenging. A different, more effective approach to signal detection may be needed, for example using real-world data from patients' records or disease databases and active surveillance systems.

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 additional considerations in this Section.

It should be considered that children and adolescents are nowadays becoming more and more involved in the shared therapeutic decision-making process and, as they are reaching adulthood, they want to engage in making their own health choices. With the increasing use of the internet, young people also tend to seek health information independently. Adolescents above 12 years of age usually take their regular medicine independently, and even younger children may learn to do so. Adolescents usually have a capacity to understand information about medicines similar to that of adults. While they typically also want to be informed comprehensively like adults, the way information is presented to them can be tailored to their interests and preferences as described below. Younger children can be approached with information in an adapted style that takes into account their information needs and capability of processing complex messages and avoids a paternalistic style. Safety communication and communication-based additional 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 age.

In order to convey information specifically of interest to the paediatric population, marketing authorisation holders and competent authorities are encouraged to address, in the product information and any additional RMM such as educational material, as appropriate, the following if evidence is available and applicable:

- 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;
- advice on the correct administration of the medicine.

Children and adolescents have different media preferences from adults and may be more effectively reached by information and educational tools like infographics, comics, video clips and social media channels adapted to their relevant age group. It is encouraged to consider this in the preparation of additional RMM. Also, additional RMM should be designed with feasibility in mind, e.g. how they can be integrated in the daily life of the young patient and how the acceptability of their use can be optimised. When preparing additional RMM, messages should be tested in conceptual, linguistic and media terms with the paediatric target group reflecting in a proportionate way the seriousness of the risk.

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, this should include advice addressing 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 follow the GVP Modules I to XVI, taking into account the considerations specific to the paediatric population in this P.IV.. The guidance in P.IV.A. should be followed for addressing paediatric-specific aspects when operating pharmacovigilance processes.

P.IV.C.1.2. European Medicines Agency

For the purpose of safe and effective use of medicinal products in the paediatric population the Pharmacovigilance Risk Assessment Committee (PRAC) (see GVP Module I) and the Paediatric Committee (PDCO) work together.

P.IV.C.1.2.1. The Paediatric Committee (PDCO)

The Paediatric Committee (PDCO) supports the development of medicines for children in the EU and its principle responsibility, among others, is to assess the content of paediatric investigation plans (PIPs) (see P.IV.C.2.) for a medicinal product.

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 (see Mandate and Rules of Procedure of the PDCO)[20].

PDCO responsibilities also include applications for a full or partial PIP waiver and for study deferrals. Waivers for the requirement of paediatric development are granted by the PDCO - in one or more specific conditions - on different legal grounds. If the specific medicinal product was waived (in accordance to Article 11(1) of the Paediatric Regulation) this aspect will be discussed by the Committee for Medicinal Products for Human Use (CHMP) at the time of assessment of the initial marketing authorisation application, with the aim to include adequate information on paediatric subjects in the summary of product characteristics (SmPC) as well as in the RMP (see P.IV.B.1.), as appropriate.

P.IV.C.1.2.2. Interaction between the PDCO and the Pharmacovigilance Risk Assessment Committee (PRAC)

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

The scope of such interaction focuses, for example, 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

[20] www.ema.europa.eu.

activities are adapted to meet the specific challenges of collecting safety data in the paediatric population.

P.IV.C.2. The paediatric investigation plan in the EU (PIP)

A PIP determines the studies that must be carried out in the paediatric population when developing a medicine. This requirement also applies when a marketing authorisation holder in the EU wants to add a new indication, pharmaceutical form or route of administration for a medicine that is already authorised and covered by a supplementary protection certificate (SPC) or a patent that qualifies for the granting of a SPC (Regulation (EC) No 1901/2006).

All applications for marketing authorisation for new medicines in the EU have to include the results of studies as described in the agreed PIP, unless the medicine is exempt because of a waiver or these are not yet available due to a deferral.

Overall a PIP is a research and development programme aimed at ensuring that the necessary data are generated determining the conditions in which a medicinal product may be authorised to treat the paediatric population. A PIP might include for example, interventional and non-interventional studies, non-clinical studies, extrapolation studies, modelling and simulation studies, development of specific paediatric pharmaceutical forms and formulations.

P.IV.C.3. The risk management plan in the EU

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

When agreeing a PIP (see P.IV.C.2.), the PDCO may (in particular with regard to knowledge gaps) identify 'Potential long-term safety/efficacy issues in relation to paediatric use for consideration in the risk management plan/pharmacovigilance activities' (included in addition to the 'Key elements' in section 5 of annex I of the PDCO opinion).

At the time of the evaluation of the submission for initial (or paediatric line extension) marketing authorisation, the applicant in the EU should evaluate whether – based on the available clinical and non-clinical evidence generated after the agreement of the PIP - such previously identified issues are still valid, and whether they should be included as important potential or identified risks in the RMP. If no information is available, but there is a potential risk related to off-label use, such potential long-term safety issues might also be considered as missing information in the RMP. The aim would be to set-up appropriate risk minimisation measures, should there be important risks related to off-label used in the paediatric population.

If there are specific safety objectives in the agreed studies of the PIP (e.g. long-term safety studies), of which results can be informative in consideration of any existing safety concern associated with the medicinal product or with any potential for paediatric off-label use, the key findings of these results should be considered for inclusion in part II, modules SVII and SVIII, of the RMP.

Furthermore, if a PIP is still to be conducted in paediatric patients following the initial marketing authorisation in adults (i.e. the paediatric clinical studies listed in the PIP opinion are deferred), it needs to be considered whether studies included in the PIP should also be reflected in the RMP taking into account important risks of the medicine related to potential off-label use in paediatrics.

All these aspects will be assessed by the PRAC and CHMP at the time of marketing authorisation.

P.IV.C.4. The periodic update safety report in the EU

Further to the guidance in P.IV.B.3., some other aspects should be considered. Significant findings arising from ongoing and completed paediatric clinical trials during the PSUR reporting interval should be included in the PSUR. This is particularly relevant when these clinical trials investigate safety objectives that are common to the agreed PIP and particularly when the PSUR submission is due before the paediatric development is completed (see P.IV.C.2.). This aims at facilitating cross-linking of information and procedures in the management of the medicinal product life-cycle.

When it is considered beneficial to gather further insight on widened use of a medicine in the paediatric population, a higher frequency of PSUR submissions as required by means in the List of European Union Reference Dates[21] might be needed (see GVP Module VII).

P.IV.C.5. Designing a post-authorisation safety study and protocol submission in the EU

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

The template for PASS protocols should be completed in accordance with guidance provided in GVP Module VIII and Guidance for the Format and Content of the Protocol of Non-Interventional Post-Authorisation Safety Studies[22], taking into account specifics for paediatrics as follows:

- template heading 8 “Research question and objectives”: this may relate to alterations in physical 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 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 weight and height in the same child which may vary in short periods of time, changes in recommended dosing as the child grows, use of age-appropriate normalised laboratory values, metabolism specificities due to maturation).

In the case of a development of a medicine to treat rare diseases in paediatric patients for which paediatric data are lacking, or very limited, registries or other means of long-term data collection could be considered by the marketing authorisation holder to enable the conduction of appropriate PASS to follow-up and appropriately document long-term safety.

In these cases, high level planning of paediatric registries and related PASS should already be considered at the time of submission of a PIP (see P.IV.C.2.), to promote continuity in the generation of safety data between the pre- and post-authorisation phase (as already highlighted in P.IV.B.4.).

The consultation of specialist networks (e.g. the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)[23]) and, where appropriate, the paediatric clinical trial networks (e.g. the European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA)[24]) could be helpful to address specific aspects related to design and conduct of

[21] www.ema.europa.eu.
[22] www.ema.europa.eu.
[23] European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), www.encepp.eu/.
[24] European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA), www.ema.europa.eu.

PASS in paediatrics. The applicants/marketing authorisation holder in the EU is also encouraged to request scientific advice (SA) from the Agency on specific aspects of PASS protocols, especially for complex or controversial issues or for innovative approaches or methodologies including those for paediatric studies[25].

P.IV.C.6. Signal management within the EU regulatory network

In addition to the guidance in P.IV.B.5., ICSRs for paediatric patients should be analysed by means of tools provided by EudraVigilance separately from ICSRs for adult patients (e.g. electronic Reaction Monitoring Reports (eRMRs)[26]).

It is recommended that statistics of disproportionate reporting (see GVP Module IX Addendum I) are calculated using only ICSRs about paediatric patients to increase the ability to detect paediatric signals of disproportionate reporting (SDR) from appropriate databases, i.e. EudraVigilance in the EU. Sub-group analysis by age and comparison of the disproportionality statistics in paediatric patients versus adults (if applicable, depending on the size of the data set) can help to determine whether or not a suspected adverse reaction is likely to be more frequent in paediatric patients.

P.IV.C.7. Safety communication in the EU

Further to the guidance in P.IV.B.5., children and their families in the EU can be consulted by the marketing authorisation holder in the EU as well as by the Agency and competent authorities in Member States through the established young person advisory groups for the preparation and revision of safety communication and educational materials for additional RMMs (see Principles on the Involvement of Young Patients and Consumers Within EMA Activities[27]). The Enpr-EMA Working Group on Young Persons Advisory Groups (YPAGs) currently works on resources and on establishing a framework of interaction, which will become available for the Agency and the EU regulatory network as well as marketing authorisation holders in the EU.

[25] Scientific advice and protocol assistance; www.ema.europa.eu.
[26] Screening for adverse reactions in EudraVigilance; www.ema.europa.eu.
[27] www.ema.europa.eu.