9 October 2018
EMA/703506/2018

Comments received from public consultation on good pharmacovigilance practices (GVP)

Product- or Population-Specific Considerations IV: Paediatric population

The draft of this module was released for public consultation between 2 August 2017 and 13 October 2017. The module has been revised, taking the comments received into account.

Those who participated in the public consultation were asked to submit comments using a specific template.

The comments received are published, identifying the sender's organisation (but not name). Where a sender has submitted comments as an individual, the sender's name is published.

The European Medicines Agency thanks all those who participated in the public consultation for their contributions.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

17 October 2017

Submission of comments on GVP Product- or Population-Specific Considerations IV: Paediatric population (EMA/572054/2016)

Comments from:

Name of organisation or individual
AESGP

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received (please see privacy statements: http://www.ema.europa.eu/ema/index.jsp?curl=pages/home/general/general_content_000516.jsp&mid *and* http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123144.pdf*).*

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF) (see Introductory cover note for the public consultation of GVP under Practical advice for the public consultation: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123145.pdf*)*
.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Line 162		Comment: Refers to 'prescribed' medicines. Suggest amendment to incorporate non-prescription medicines for completeness. Proposed change (if any): prescribed to be replaced by 'used'	
Lines 224-225		Comment: There is discussion of improving AE reporting of off label use in paediatrics but it is not clear what aspect is trying to be improved	
Lines 263-264		Comment: With reference to the bullet below, it can be important for some products to consider whether dosing in paediatrics should be based on weight or age. It would be helpful to highlight this point as a consideration for using products safely & effectively in children. - *weight and height, as these can vary considerably across an age group and influence the susceptibility to an adverse reaction.* Proposed change (if any): add reference to age as sometimes more appropriate	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Lines 269-274		Comment: This seems out of position & may be better under section B.5	
Line 287		Comment: Difficult to read, quote marks around ‘not age appropriate’ would help.	
Lines 290-291		Comment: How can paediatric exposure be measured if the product is used off label (i.e. no paediatric indication)?	
Section P.IV.B.5		Comment: Suggest adding mention of the need for paediatric exposure data to provide context for signals.	

Please add more rows if needed.

06 October 2017

Submission of comments on GVP Product- or Population-Specific Considerations IV: Paediatric population (EMA/572054/2016)

Comments from:

Name of organisation or individual
AstraZeneca Pharmaceuticals

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received (please see privacy statements: http://www.ema.europa.eu/ema/index.jsp?curl=pages/home/general/general_content_000516.jsp&mid *and* http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123144.pdf*).*

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF) (see Introductory cover note for the public consultation of GVP under Practical advice for the public consultation: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123145.pdf*)*
.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Page 7 , after line 186		Comment: Proposed change (if any): Please consider adding a bullet point stating: Long term consequences on reproduction organs.	
Page 9, line 286		Comment: Proposed change (if any): Please consider deleting the word “substantial”. Substantial can be interpreted as a large number and in the pediatric population those rarely exists and therefor there is a risk of missing important data if substation is kept in that sentence.	
		Comment: Proposed change (if any):	

Please add more rows if needed.

17/10/2017

Submission of comments on GVP Product- or Population-Specific Considerations IV: Paediatric population (EMA/572054/2016)

Comments from:

Name of organisation or individual
Dutch Medicines Evaluation Board

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received (please see privacy statements: http://www.ema.europa.eu/ema/index.jsp?curl=pages/home/general/general_content_000516.jsp&mid *and* http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123144.pdf*).*

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF) (see Introductory cover note for the public consultation of GVP under Practical advice for the public consultation: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123145.pdf*)*
.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Line 39-44		Comment: Several subsets of the paediatric population are classified as defined e.g. in international guidelines. Proposed change (if any): It could be considered to indicate in line with the original publication referred to that: “It may be appropriate to use different subsets (e.g. based on gender or stage of pubertal development), but the choice of subsets should then be sufficiently explained and justified.”.	
Lines 138-139		Comment: Medication errors regarding paediatric use are sometimes difficult to avoid, because the products are developed and authorised for adults. Meaning when the product may be prescribed off-label to a child. Proposed change (if any): Addition of the often off-label prescription for children and medication errors. Inappropriate route of administration or pharmaceutical form, and dosing inaccuracy in children are relevant issues both for medication errors and off-label use.	
Lines 201-211		Comment: Regarding PASS Proposed change (if any): An example for such a PASS could be a registry with follow-up to study for instance the long-term safety in case of chronic use. This might be included.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Lines 330		Comment: … or physical development. Proposed change (if any): Should this be 'neurological development'? if not please add 'neurological development.	
Line 366		Comment: Regarding subgroup analysis by age … Proposed change (if any): The message that it is important to collect complete information about age to be able to perform such analysis could be repeated here.	
Lines 370-371		Comment: "……, should be lower than that for the whole population." This should be deleted and reworded, because for certain drugs the proportion of children taking a medicinal product can be higher than adults. Proposed change (if any): Reworded text could be: 'adapted for the exposure in children.'	
Line 372-373		Comment: Regarding "……. and a follow-up strategy should be in place to consistently complete ICSR with essential information .". Proposed change (if any): This may be further clarified as it is unclear to what kind of strategy is meant. Does this for instance mean that there should always be some kind of a targeted-questionnaire in place that should be used for	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		paediatric case reports?	
Line 405		Propose to add 'birth control pill'.	
Lines 407-409		Comment: New educative tools such as social media are suggested to be more effective in younger people and we agree that they seem promising. Proposed change (if any): It would be helpful to provide more concrete examples of new educative tools (social media, apps) that have been successfully implemented. Further, the need of user testing in advance should be emphasised as there is limited experience with these tools so far in pharmacovigilance. Adequate and adjusted measures to evaluate these new educative tools should be proposed.	

Please add more rows if needed.

<Date of submission>

Submission of comments on GVP Product- or Population-Specific Considerations IV: Paediatric population (EMA/572054/2016)

Comments from:

Name of organisation or individual
[redacted] Centre Midi-Pyrénées de PharmacoVigilance, Toulouse

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received (please see privacy statements: http://www.ema.europa.eu/ema/index.jsp?curl=pages/home/general/general_content_000516.jsp&mid *and* http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123144.pdf*).*

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF) (see Introductory cover note for the public consultation of GVP under Practical advice for the public consultation: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123145.pdf*)*
.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	This document is comprehensive. Just some comments: - P.IV.A.1.3: what about medication errors without adverse drug reactions? Is it planned to enter them in pharmacovigilance databases? - P.IV.A.1.4: As regards off label use, what about drugs with quality evidence supporting their use. The term of off-label should be clearly defined. - P.IV.B.2: In the “real word”, information such as indication, doses, duration of exposure are often missing in ICSRs. Moreover, it is difficult to obtain these data “a posteriori”. Use of a quality score such as Vigigrade may be a motivating factor! P.IV.B.6: I agree that communication is important, nevertheless, the first step is to obtain high quality data.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
	Line 57	Comment: What is the reference of “number of change”? Proposed change (if any):	
	Line 90	Comment: Is pediatric population differenciated in GVP PI? Proposed change (if any):	
	Line 98	Comment: The reference “Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental Pharmacology – Drug Disposition, Action, and Therapy in Infants and Children. N Engl J Med 2003;349:1157-1167 “ could be added. Proposed change (if any):	

Please add more rows if needed.

12 October 2017

Submission of comments on GVP Product- or Population-Specific Considerations IV: Paediatric population (EMA/572054/2016)

Comments from:

Name of organisation or individual
European Association of Hospital Pharmacists (EAHP)

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received (please see privacy statements: http://www.ema.europa.eu/ema/index.jsp?curl=pages/home/general/general_content_000516.jsp&mid *and* http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123144.pdf*).*

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF) (see Introductory cover note for the public consultation of GVP under Practical advice for the public consultation: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123145.pdf*)*
.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	EAHP overall agrees with the content of the Guideline on good pharmacovigilance practices - Product- or Population-Specific Considerations IV: Paediatric population. The guideline covers all important aspects, wherefore EAHP does not have any specific comments on the text.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		Comment: Proposed change (if any):	
		Comment: Proposed change (if any):	
		Comment: Proposed change (if any):	

Please add more rows if needed.

12.9.2017

Submission of comments on GVP Product- or Population-Specific Considerations IV: Paediatric population (EMA/572054/2016)

Comments from:

Name of organisation or individual
EFPIA [redacted]

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received (please see privacy statements: http://www.ema.europa.eu/ema/index.jsp?curl=pages/home/general/general_content_000516.jsp&mid *and* http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123144.pdf*).*

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF) (see Introductory cover note for the public consultation of GVP under Practical advice for the public consultation: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123145.pdf*)*
.

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	The EMA's efforts to provide guidance on good pharmacovigilance practices in special patient populations are supported by EFPIA and we welcome the opportunity to participate in the current stakeholder consultation. In evaluating the document, however, we noted there is not a lot of new or updated information regarding pharmacovigilance in the paediatric population. Rather, the Guideline appears to serve mainly as a central repository of instruction and advice already provided in existing regulatory formats, such as the RMP and PSUR GVP modules. If this is the primary objective, we recommend that it be explicitly stated in the Introduction section. If the intent is also to introduce additional guidance to sponsors for conducting paediatric pharmacovigilance, we believe there are multiple areas of the document that could benefit from additional detail and clarification and from the agency's endorsement of actual pharmacovigilance tools and methodologies. These are addressed in Section 2 of this template under "Specific Comments". Accepted methodologies to "adapt" the safety information from adults to paediatric population should be proposed / included as guidance for the MAH. When the consultation of the ENCePP, Enpr-EMA and YPAG is suggested; the criteria, specific situations, process and timelines when these groups should be	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	consulted is missing. If the process timelines by consulting the specified groups are affected, that information needs to be included. Specific criteria on the lowering of signal threshold and to increase the frequency of submission PSURs need to be provided. The guideline would benefit significantly from text further describing its intended applicability. Clarity is needed on what requirements are applicable to all products and which ones are required only when there is a paediatric indication / evidence of use. It would be helpful if the sections in P.IV.B could clarify what is new guidance versus what is already contained in GVP Module I through XVI. EFPIA would welcome an opportunity to discuss with the agency and other stakeholders the major points and suggestions presented in this response.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
41		**Comment:** The ICH E11(R1) Guidance *Step 4* has provided an updated definition of neonate as follows: *Neonates include term, post-term and preterm newborn infants. … The neonatal period for preterm newborn infants is defined as the day of birth through the expected date of delivery plus 27 days*. Therefore, the draft Guideline definition of preterm neonates (from 0 to 27 days) is no longer consistent with the international standard, and should be amended to better facilitate harmonized global pharmacovigilance practice. **Proposed change:** Consider amending the Guideline definition to reflect ICHE11(R1)	
42		Current text line 42 doesn't specify the number of days corresponding for 1 month. **Proposed text: 1 month (28 days)**	
84-85		**Comment:** please consider inclusion of the sponsor of clinical studies among stakeholders **Proposed change** (if any): please see above	
93-98		**Comment:** Not all subsets of the paediatric population "differ substantially" from adults as they relate to distinct PK and PD characteristics (Lines 97-98). In 2013, the FDA published an analysis of 126 unique molecular entities with paediatric studies submitted to the FDA after 2007 *(Momper et al. Adolescent Dosing and Labelling Since the Food and Drug Administration Amendments Act of 2007. JAMA Pediatr. 2013;*	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		167(10): 926-932.). The authors found that for certain diseases occurring in adults and adolescents, there may be little difference in renal capacity or hepatic enzyme expression leading to a high degree of congruence on dosing. **Proposed change:** Consider amending the text to reflect that there may be *subsets* of a paediatric population that differ substantially from adult populations due to their "distinct PK and PD characteristics". This is an important factor influencing both the "susceptibility" of the paediatric population to adverse reactions, and in considering the variety of PV activities that could be conducted across the paediatric population.	
92-117 (or 172 – 193)		**Comment:** Post-pubertal children may not be very different from adults. **Proposed change:** It might be useful to acknowledge this. E.g.: "When it is anticipated that a subgroup of the paediatric population will likely not be different from the adult population (e.g. post-pubertal children, children above a certain age and/or weight, this should be called out and dully justified".)	
Lines 101 - 104		**Comment:** No consideration of maturing immune system (transition from passive maternal immunity conferred transplacentally to maturing innate & adaptive immune systems in infants) among other organ systems – this should be an important factor to consider in assessing impact of medicines on infective/ hypersensitivity adverse reactions. **Proposed change** (if any):	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		Add specific mention of changing immune system physiology in children. Same consideration could be applied to lines 187 – 193.	
102		**Comment:** Considering the metabolic activity of the bone during the growing process and the potential impact of medicinal product that may have a cumulative effect, the bone should be added. **Proposed change:** (…brain and blood-brain barrier, bone as well as …)	
111		**Comment:** We note that while long- term effects on development are an important concern in pharmacovigilance, the challenges of attributing any shorter-term drug exposure to a concern years to decades later are extraordinary and are confounded by other factors, especially if the negative effect is not an overt one. **Proposed Change:** Add a sentence acknowledging this challenge in this bullet.	
132-145		**Comment:** We suggest that the paediatric population faces risk of harm mainly by misuse, abuse, accidental exposure and overdose of medicines, often due to unavailability of appropriate paediatric formulations, rather than strictly through the more generic label of “medication errors” used in the Guideline. There is a need for practical advice on how to implement monitoring and proposed preventability of these potential and identified harms. **Proposed Change:** Consider including specific guidelines on how to detect, where to document, and how to measure preventability of harm, e.g. the Risk Management Plan. Also, there is a potential difference on the risk of misuse or	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		overdose in compounds which have paediatric indication and those used in off-label use. This should be highlighted.	
149		**Comment:** The off-label use in paediatric population includes use in non-authorised paediatric age categories, but also non-authorised dosing or administration schemes, which should be included. **Proposed change:** (…authorised paediatric age categories (see GVP Annex I) and non-authorised dosing or administration schemes.)	
159		**Comment:** please consider replacing “and” with “or” **Proposed change** (if any): “…risk of adverse reaction OR a lack of therapeutic effect.”	
163		**Comment**: It is difficult to interpret this section as the information provided is rather superficial and the intent is unclear. Paediatricians are meant to identify different symptoms in the different age groups and in verbally uncommunicative patients (e.g. the mentally disabled) that can also be found also in the adult population. Moreover, in younger age groups the detection of adverse events usually remains with the parents/care takers. It needs to be highlighted that adverse events related to drug may not be identified if they are not suspected to be causally related by the parents/care takers. Consider adding a clarification to indicate if this section of the guidance is included only as a reminder or if the intent is to deliver specific instructions. If the latter, there needs to be further explanation of the regulatory expectations. Also, consider highlighting the medical impact of failure by parents and caregivers to recognize adverse events and list possible solutions and the need for the use of objective	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		measures such as scales.	
168		**Comment:** Crying in infants and toddlers might be caused by an underlying illness but can also occur as a result of stress, fear, etc. This would make it practically impossible to differentiate it from an AE. This line as it is would leave room for interpretation with potentially some MAHs reporting 'crying' as AE whereas other MAHs wouldn't do it, which is the reason why crying should be removed. Also, "Dizziness" is a symptom and not an appropriate example here: infants and toddlers who do not yet have sufficient language development will not be able to complain about "dizziness". **Proposal:** (…infants and toddlers, such as vomiting and diarrhoea are non-specific and…)	
Lines 178-179		**Comment:** The original wording ("appraised," "some") suggests that the activity is discretionary. This should be a mandatory, systematic and comprehensive assessment given that this is talking about children's health and adult solutions are wholly applicable. Proposed change (if any): "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~~ **should be evaluated and adapted, as needed,** to target paediatric patients more effectively."	
179		**Comment:** Further guidance should be given on how to prevent or minimize risks. (i.e.: Educational materials addressed to	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		parents and adolescents taking contraceptive products that are acquired without medical supervision).	
193		**Comment:** Considering the metabolic activity of the bone during the growing process and the potential impact of medicinal product on it, the bone should consider. **Proposed change** (if any): - susceptibility to adverse drug reactions of musculoskeletal system only during active growth phase.	
199		**Comment:** Reference is made to reference number 14 but there is no reference 14 provided on this page.	
201-211		**Comment:** This section implies that a PASS may be appropriate any time an adult-to-paediatric extrapolation is made. As extrapolation is used when the available paediatric population for study may be limited in number, and therefore we note that a study may prove to be very difficult to recruit subjects for and also to complete. In addition, extrapolation is still a new concept. As more and more PIPs will make use of this tool, in often crowded disease areas, there could be potentially a large number of those being run with the likelihood of completion even more remote. **Proposed Change:** Re-consider if extrapolation of adult data is a specific criterion for PASS. Regarding the statement "*the paediatric clinical development and the application for a paediatric indication relies heavily on extrapolation of adult or paediatric sub-group efficacy data*,"	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		please clarify why extrapolation of efficacy data would constitute a requirement for PASS rather than PAES.	
212-232		**Comment:** The Paediatric Regulation 1901/2006 has been in force since 2007, and since that time the EMA has agreed on average about 90-100 new industry paediatric plans annually (2016 EMA Annual Report to the EC). Given the sheer number of approved paediatric plans, "spontaneous reporting of adverse reactions collected during the post-authorisation phase" should not be the "only available primary source of information on adverse reactions" in the paediatric population. **Proposed change** (if any): Consider addressing in this section of the guideline how more meaningful methods of prospective safety analysis in the context of paediatric investigation plans (PIPs) could ensure a more robust and controlled method of capturing safety data to better inform what kind of post-authorisation safety activities are required for paediatric populations.	
213		**Comment:** Specific forms for the collection of AE in paediatric population should be designed and make them available to reporters.	
215		**Comment:** cross reference in brackets is made to P.IV.B.2. while in P.IV.B.2 section. **Proposed change** (if any): Provide correct cross reference to P.IV.B.5	
Lines 224-225		**Comment:** It is not clear what this sentence means. There is discussion of improving AE reporting off label use in paediatrics but it is not clear what aspect is being improved or what the drafting group has in mind.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		Proposed change: Please include clarification and additional details.	
242		**Comment:** Reference is made to five paediatric age groups. However, the EU definition quoted in Lines 38-44 only mentions four age groups. **Proposed change** (if any): Change text in Line 242 to refer to **four** paediatric age groups. Alternatively, If pre-term neonates are to be considered a separate group from term neonates, consider making this explicit in a statement and revise lines 38-44 for consistency.	
248		**Comment**: We believe information about cognitive and motor developmental milestone should also be collected. **Proposed change:** Consider adding "cognitive and motor developmental milestone" to the text.	
249-250		**Comment:** In the introduction section, it is clearly stated (88 – 90) that exposure of medicines in utero is outside the scope, however in lines 249 to 251 it is suggested that this information should be obtained for the ICSR. **Proposed change:** Scope of this guidance should be clear and consistent throughout the document. **Comment:** Exposure through breast feeding is an important route of exposure.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		Proposed Change: Add breast feeding e.g. "... information on maternal and paternal exposure during conception and on pregnancy **as well as exposure through breastfeeding** may also be of relevance ..."	
257		**Comment:** In order to align with P.IV.B.2.1 in which it is stated that "As far as possible the ICSRs should indicate" perhaps in line 257 "Paediatric ICSRs should also include high quality data on" should be rephrased to "As far as possible paediatric ICSRs should…."	
252-255		**Comment:** For neonates, information regarding birth history is important and should also be collected. **Proposed change:** Consider modifying the text to read: "Additionally, information on birth history as well as major developmental parameters should be collected".	
260		**Comment:** As the administration scheme can be a relevant factor to the development of ADR in paediatric population, specially related to off-label use, this should be included as specifically relevant information. **Proposed change** (if any): (…) total daily dose as well as administration scheme), … **Comment:** When reporting an AE/overdose/medication error/lack of drug effect, the method of how the dose was calculated (i.e.: age, weight) should be included, as it frequently can lead to overdose/under dose. Additionally, information about treatment compliance should be included.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		Proposed change (if any): (...duration and circumstances of exposure, method to calculate the dose, treatment compliance, including…)	
263		**Comment:** Weight and height can vary significantly within a short period of time specially in infants and toddlers, having an impact on the distribution of drugs. Therefore, the weight and height at the time of reaction is presented is relevant. Also, “length” is used for infants and not yet standing young children **Proposed change:** Addition of ‘at time of reaction’. (...weight and length/height at time of reaction, as these can vary considerably across...)	
Lines 269-274		**Comment:** This text is out of position and is better included in section B.5	
269-274		**Comment:** The potential regulatory expectations for alternatives to signal detection are somewhat ambiguous. This section would benefit from practical guidance and specific examples.	
269 - 274		**Comment:** The use of real-life data from patient’s records or disease databases and active surveillance systems is recommended. However, this will very often not be possible due to personal data protection legislation. **Proposed change (if any):** Add a comment that personal data protection legislation should be taken into account when looking for additional ways to collect relevant safety information.	
276		**Comment:**	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		Missing word? Proposed change highlighted below. Proposed change (if any): "The requirements for periodic safety update reports (PSUR) included **in** GVP Module VII should be followed."	
Lines 278-280		**Comment:** More a feedback than a clarification. The PSUR is a global document, so if a paediatric indication is approved even if outside of the EU, benefit-risk will be considered as the PSUR is written to the core information for a product and covers all global regions.	
278-282		**Comment:** While presenting safety data in the PSUR of products with an indication in both paediatric and adult population, the emphasis should be to present safety data based on age (and when feasible paediatric sub age groups) for the safety topics.	
283-289		**Comment:** Is this statement indicating that if any cases of ADRs have been reported in the safety database, separate sections of the PSUR are required? The standard approach is to monitor all information and describe any signals noted, including those in the paediatric population (for a medicine without an approved paediatric indication this may be covered as off-label use, missing information, or through presentation of outcome of routine signal detection activities). **Proposed change:** Please clarify if this guidance requires separate subsection for the paediatric population in certain circumstances and if yes, specify what those circumstances are to avoid ambiguity. **Comment:** Regarding the bullet point “paediatric adverse reactions have	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		been previously reported," it would be useful to have more guidance, as the current statement does not provide any qualifiers. This information would be most relevant to present when a signal of an adverse reaction unique to paediatrics has been identified. **Proposed change:** Consider replacing line 289 with "a signal of paediatric adverse reactions has been identified."	
283-289		**Comment:** Technically, there could be a grey area because the existence of a paediatric indication doesn't necessarily mean the indication is approved for all of the paediatric sub age groups. **Proposed change** (if any): Clarification that, where applicable, discussion and analysis of the use of the drug in paediatric age groups should also include those paediatric age groups for which there is no approved indication.	
286		**Comment:** The term "substantial paediatric use in the absence of a paediatric indication" may be ambiguous and subject to interpretation. **Proposed change (**if any): Clarification as to what should be considered "substantial paediatric use in the absence of a paediatric indication" would be useful.	
Lines 286-299		**Comment:** We do not have a concern with this statement or the current phrasing. As noted the legislation already notes that agencies can request different frequencies based on safety concerns	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		that might include paediatric, so this does not change the existing approach.	
290-292		**Comment:** Regarding the statement "*Furthermore, information on: the number of paediatric patients exposed during the reporting period and the method of exposure calculation,*" it would be useful to clarify that this information is required when applied to lines 285-289. **Proposed change:** Consider replacing line 290 with "In such scenarios, the information on: …"	
291-292		**Comment:** Regarding the statement "*the number of paediatric patients exposed during the reporting period and the method of exposure calculation,*" it would be useful to acknowledge that paediatric exposure data for the post-marketing setting for product with no paediatric indications may not be available. There are considerable limitations in estimating paediatric exposure mainly because of off label use and this should also be acknowledged. **Proposed change:** Consider adding to line 292 (*text adapted from GVP Module VII*): "Although it is recognised that it is often difficult to obtain and validate exposure data, the number of paediatric patients exposed should be provided whenever possible, along with the method(s) used to determine the estimate. Justification should be provided if it is not possible to estimate the number of paediatric patients exposed." It would be helpful to include more guidance (if available) on how to assess paediatric exposure if the product is used off-	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		label.	
Lines 296-299 & Lines 449-451		**Comment:** Regarding the frequency of reports, recommend aligning with language in GVP module VII - Periodic Safety Update Report (Rev 1) section VII.C.3.4 **Proposed change:** "…this may lead to a requirement for a higher change in frequency of PSUR submissions…"	
310-313		**Comment:** The statement "*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)*" is difficult to understand. The confounding concept as applicable to studies in non-interventional setting does not appear to be used correctly when referring to potential misclassification related to imprecise diagnostic coding etc. **Proposed change:** If another meaning is intended, please consider clarifying.	
310-314		Wording unclear. Proposed changes highlighted below. Proposed change (if any): "… that may ~~lead~~ **result** in confounding ~~due to~~ factors relating to child development …"	
314-316		**Comment:** If "challenges" for "feasibility" means not do-able, how is this expected to be "addressed in a PASS protocol demonstrating that they will be appropriately managed"? Non-feasibility itself is beyond a limitation.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		Proposed change: Additional clarification is required.	
Line 318		Delete the word 'of' in the following clause: "…but because <u>of</u> the inclusion of paediatric patients…"	
322-325		**Comment:** Missing words? Proposed changes highlighted in red font below. **Proposed change** (if any): "An early planned study would facilitate **the** understanding ~~**on of**~~ **the** possible types of data that can be gathered after marketing authorisation and can support in defining **the** main characteristics and requirements for paediatric registries that can be set-up more promptly, enabling **them** to address research questions arisen in the pre-marketing phase."	
331-333		**Comment:** Wording unclear. Proposed changes highlighted below. **Proposed change** (if any): "... 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 ..."	
339		**Comment:** Consider requiring that age-appropriate normal laboratory values should be used as reference while analysing safety signals arising for laboratory abnormalities.	
Section P.IV.B.5 (Lines 339 – 384)		**Comment:** It is suggested to add mention of the need for paediatric exposure data to provide context for signals.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
340		**Comment:** We note that National healthcare or hospital systems or such regional/population databases also give rise to signals in paediatric patients with potential AEs and contain data on documented prescriptions. These can be a valuable source of information for signal detection activity. The potential value of Big Data with evolving technologies e.g. I2B2 in this space could be enormous if done well. **Proposed change:** Consider adding text on using these resources to augment in-house signalling activities.	
348		**Comment:** We believe that vaccines generally require a different set pharmacovigilance activities from medicines and are not a relevant example for this section. **Proposed change:** Consider deleting vaccines as an example.	
352		**Comment:** Proposed clarification highlighted below. **Proposed change:** "Hence, ~~performing~~ **if** paediatric statistical signal detection **is performed, it** may benefit from ...".	
355-356		Comment: Proposed clarification highlighted in red font below. **Proposed change:** "... aim firstly at addressing whether an adverse reaction is new or more severe **or more frequent** than previously known **or differs in reversibility**, in one or all paediatric age	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		groups."	
367-368		**Comment:** Proposed clarification highlighted in red font below. **Proposed change:** "... disproportionality statistics in paediatric patients versus adults **(if applicable, depending on the size of the data set)** can help to determine ..."	
364-365		**Comment:** This statement should make a clear reference to GVP Module IX Addendum I on signalling (current draft). It should be clarified that routinely generated signalling reports from Eudravigilance include statistics of disproportionality in sub-populations (paediatric and geriatric). GVP Module IX text should be completely aligned to this text. **Proposal:** 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 appropriate** ~~spontaneous~~ **databases** ~~such as~~ **i.e. EudraVigilance.**	
367-369		**Comment:** Regarding the statement "*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*", it would be useful to add more guidance under which assumptions the comparison may be valid and to acknowledge a potential for misuse or misinterpretation of disproportionality analysis if	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		such comparison is used as a blanket approach without considering the reporting mechanisms that may contribute to apparent disproportionality between children and adults. **Proposed change:**Add more guidance under which assumptions the comparison may be valid and to acknowledge a potential for misuse or misinterpretation of disproportionality analysis if such comparison is used as a blanket approach without considering the reporting mechanisms that may contribute to apparent disproportionality between children and adults **Comment:** The qualitative differences in reporting for paediatric patients as highlighted in the remainder of the section suggest that the interpretation of such a comparison as differences in event frequencies may be generally inappropriate. **Proposed change:** Consider deleting statement or mentioning the potential limitations / sources of bias inherent in this approach.	
370-373		**Comment:** Having a different case count threshold for pediatric cases versus adult for signal detection would be difficult to implement into signal detection systems. It is certainly appropriate, upon identification, to have a lower threshold for pursuing a pediatric issue, and a low case requirement for validation and assessment, but this would be after identification and relate to the qualitative assessment of the issue. **Proposed change:** We recommend EMA not to be prescriptive on the signaling	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		threshold but to allow companies to define methodology for signal management activities focusing on the paediatric population.	
375 - 377		**Comment:** Stratification (by age in the case) is only useful if there are sufficient cases in each group. With the usually (very) low numbers of paediatric patients, the likelihood of getting meaningful information out of subgroup analysis is very low. **Proposed change:** Acknowledge this limitation.	
381-384		**Comment:** It would not be possible to implement this as a standard across all products. We suggest to EMA to make it clear that this would be for specific situations, and they would be defined in something like an RMP. There are situations that would require this level of surveillance, but it should be clear that this is not an expectation across all drugs and all events. **Proposed change:** As stated in the comment above.	
385		**Comment:** There should be some discussion on application of paediatric patient preference, burden of additional Risk Minimisation Measures and overall Benefit-Risk acceptability from a paediatric perspective. (refer to line 497)	
385-417		**Comment:** The recommendation to consider alternative media (comics, infographics, apps, online videos, etc.) is valuable. However, additional guidance would help MAHs to successfully create and implement targeted safety communications via alternative media while complying with current policies. GVP Module XVI explicitly describes educational materials that are "fully	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		aligned" with the currently approved SmPC and PL, which may not be the case with the safety messaging topics described in this document (i.e., decreased exercise stamina). In addition, GVP Module XVI describes removal of "direct or veiled" promotional elements including "suggestive images and pictures" from any educational materials. The safety communications section in this document, however, describes the use of images and pictures via comics, apps, infographics to communicate to paediatric patients. **Proposed change** (if any): Examples of best practice for alternative media would be useful in supporting MAHs to explore this new educational tool while remaining in compliance with the policy described in GVP Module XVI.	
392		**Comment:** The age group referred to here appears inconsistent with the definition in Lines 38-44. Proposed change to wording highlighted below. Proposed change (if any): "~~Children~~ **Adolescents** above 12 years of age usually take ..."	
Lines 399-400		**Comment:** This statement suggests that EMA is advocating a 'shared decision-making approach.' If so, it would be valuable for the guidance to cite one or more sources that set forth best practices in engaging in shared decision-making. In addition, it would be important here for the EMA to clarify whether they are advocating for HCPs to use a shared decision-making approach or for sponsors, when designing risk communication and risk minimization materials, to	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		incorporate more of a shared-decision making model. **Proposed change:** Please cite one or more sources that set forth best practices in engaging in shared decision-making. Clarify whether they are advocating for HCPs to use a shared decision-making approach or for sponsors.	
406		**Comment:** NCA should make sure that relevant safety information are available for products that can be used without medical supervision, as these drugs are usually self-administered by adolescents (e.g. contraceptives). **Proposed change** (if any): (…choice, involving the child as appropriate to their age. **National Competent Authorities should assure that adequate communication channels & related safety information is available for medicinal products that do not require medical supervision (e.g. contraceptive products, including day after pill).)**	
Lines 407-409		**Comment:** Recommend adding in a reference to using comic book-type communications, and gamification methods as effective educational tools for children. **Proposed change:** As mentioned in the comment	
407-409		**Comment:** Use of the phrase “younger people” could refer either subsets or the entirety of the paediatric population. If it is meant to imply the broader paediatric population, there should be further guidance (regulatory and legal) provided on appropriate methods of direct-to-paediatric-“consumer” methods to ensure that the information and educational tools	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		are appropriate for this type of interaction.	
417		**Comment:** The issue concerning drug dependency, abuse or misuse is an important concept for this section. It is particularly important when drugs are self-administered, especially by the adolescent age group, without parental supervision. **Proposed Change:** Consider adding text to reflect these additional concerns.	
434-440		**Comment** As currently written, this section of the guideline can be interpreted to mean EMA's Paediatric Committee is unilaterally making recommendations on paediatric development, without input from other agency functions. **Proposed change:** Please clarify if this is the intent or if other subject matter experts within the agency will be involved.	
455-456		**Comment:** Regarding the statement "*long term follow-up and maintenance of registries to document the long-term outcome should be considered by the marketing authorisation holder(MAH),*" it would be useful to acknowledge that long-term follow-up through the means of a designated registry may not always be feasible for all patient populations and alternative means for data collection should also be considered. **Proposed change (if any):** Replace line 455 with "*long term follow-up and maintenance of registries or other means of data collection to document the long term outcome…*"	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
457-461		**Comment:** This paragraph's text implies that deferred studies that have been agreed to in the PIP are to be reviewed at the time of the initial marketing authorisation. Please clarify the purpose of the review at this point, by whom it should be carried out and if the expectation is that all deferred studies are to be included in the RMP as PASS.	
496		**Comment:** The text is in error when it states that paediatric requirements in the post-authorisation phase apply to medicines that are covered by intellectual property rights. This is not entirely correct; the requirement applies only to medicines protected by a SPC or a patent that qualifies for a SPC (article 8 of the Paediatric Regulation (EC) No 1901/2006). **Proposed change:** Consider replacing "*intellectual property rights"* with "*a SPC or a patent that qualifies for a SPC".*	

Please add more rows if needed.

October 13, 2017

Submission of comments on GVP Product- or Population-Specific Considerations IV: Paediatric population (EMA/572054/2016)

Comments from:

Name of organisation or individual
[redacted] EUCROF, Paediatric Working Group (PWG)

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received (please see privacy statements: http://www.ema.europa.eu/ema/index.jsp?curl=pages/home/general/general_content_000516.jsp&mid *and* http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123144.pdf*).*

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF) (see Introductory cover note for the public consultation of GVP under Practical advice for the public consultation: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123145.pdf*)*
.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Lines 37-90		Comment: P. IV.A. Introduction: Adverse reactions to medications are specific in nature in terms of symptomatology and the specific age related physiology and metabolism involved in drug absorption and subsequent effects in the paediatric population. The need for specific research directed to understanding adverse drug reactions in children of various ages is therefore, inherent and thus, research efforts as well as necessary funding must be clearly defined and focused, i.e. children oriented research. In essence, research conducted in adults can provide orientation of specific drug reactions or adverse effects but clinical trials must be conducted in children with specific measurable outcomes or endpoints in order to be incorporated into everyday clinical practice. The use of “off-label” medications in the paediatric population draws concerns as to proper dosing, indications, and the possibility of more severe adverse reactions due to the relatively unknown nature of the medication itself as well its effects in the paediatric population; which includes a broad range of ages from preterm neonates to adolescents on the verge of entering adulthood. It seems that specific EU legislation passed in July 2012 takes these factors into consideration and hence, the current document (GVP) was revised in this spirit as well. There does not seem to be a need to add or make any changes to this document as the important aspects of conducting research in the paediatric population seem to be taken into consideration.	

		Proposed change (if any):	
Lines 91-117 Lines 118-132		Comment: P.IV.A.1. Pharmacovigilance aspects specific to the paediatric population P.IV.A.1. Susceptibility to adverse reactions This section reiterates what has already been stated above but delving into more specifics or growth and maturation of organ systems that of course are very age specific. Skeletal growth, sexual maturation, neurological growth are some factors that come to mind which can be severely impacted or affected by improper drug administration. P.IV.A.1.2. Limited numbers of subjects in paediatric clinical trials This section covers the importance of robust data sets with statistically powered results in order to yield value information about adverse drug reactions in the paediatric population. Without high-powered statistical studies with large data sets it is difficult to measure or draw definitive conclusion related to adverse drug effects. The overall aim is to establish large databases for clinicians and researchers for reliable information to guide clinical practice and research. Proposed change (if any):	

Lines 132-145		Comment: P.IV.A.1.3. Medication errors This section states that medication errors are three times more frequent in occurrence in the pediatric population than in the adult population and the consequence are more significant as well. Error reduction strategies are clearly needed, however, are not specifically addressed in this document. Medication errors can occur in prescribing, dispensing, storing, preparing and administering a medicine. The recent commercial increase in the number of over the counter products aimed toward the paediatric population should be assessed for the number of adverse reactions that some of these products may have brought about. How many cases of these types of medication errors have been reported? Proposed change (if any):	
Line 146-162		P.IV.A.1.4. Off-label use The use of off-label medications in the paediatric population has clearly negative effects that often outweigh the potential positive therapeutic benefits. Ideally all medications prescribed to children should be clearly indicated for the particular age group and conditions with known adverse effects. In essence, the elimination of all off-label medications if feasible would prevent many adverse reactions, fatalities, and create an overall safer environment for the care of children. Perhaps, legislation should be enacted to achieve such goals. Proposed change (if any):	
Line 163-170		Comment: P.IV.A.1.5. Clinical presentation of adverse reactions Adverse reactions to medications can be more difficult to recognize in the paediatric population due to variations in cognitive and emotional development. Older adolescents perhaps will be more able to define their symptomatology whereas younger children may be less able to. Clinical signs of vomiting, nausea, diarrhea, headache, joint or abdominal pain usually will be recognized by the clinician, however, more specific symptoms especially psychiatric such as delusional thinking, hallucinations, etc. may not be readily diagnosable especially if the underlying or initial diagnosis is not clearly defined. Again the elimination of off-label drug use will aid to decrease the incidence of adverse reactions. Proposed change (if any):	

Line 171-211		Comment: P.IV.B.1 Structures and processes P.IV.B.1 Risk management plan The utilization of knowledge from the adult population as to adverse drug effects in the paediatric population for risk management planning cannot be fully relied upon since there might not exist any previous experience in the adult population. Furthermore, as has been previously stated drug interactions are different in children than in adults due to developmental changes and variable degrees of maturation in children. Some important aspects discussed here are: -Variable degrees of GIT maturation that can influence absorption and distribution of the pharmacologic agent and as well as the therapeutic effect. -Structures such as the blood-brain barrier in which certain drugs can pass through and others will not; and also dependent on liver function (P-450) and overall absorption, metabolism, distribution, etc. Juvenile Animal toxicology studies are also mentioned as providing possible models for understanding drug interactions in the paediatric population. Proposed change (if any):
Line 212-232		P.V.B.2 Management and reporting of adverse reactions This section emphasizes the importance of spontaneous reporting of adverse reactions in the paediatric population especially in the context of off-label medications. Ideally, a large database of information should be collected and used to assess medication risks in children. Together with the concept of signal identification, which generally implies any abnormal reactions or changes in physiology of any kind should also be recorded. Perhaps, more emphasis should be placed on clear steps necessary to achieve such a database including access and conditions of use taking into consideration patient identity and respecting medical confidentiality as well. Proposed change (if any):
Line 233-255		P.IV.B.2.1. Age information This section considers the importance of reporting patient's age in the individual case safety reports (ICSR) as accurately as possible in order to account for variations in physiological development of cellular metabolism, receptor expression, receptor activity, etc. The age of the child at the onset of the adverse reaction should be reported in order adequately follow the patient's course to recovery or whatever the outcome may be. Any patterns of the reaction may also be documented for future clinical reference. The issue of patient confidentiality must again be insured and respected. Proposed change (if any):

Lines 256-274		Comment: P.IV.B.2.2. Other specifically relevant information This section covers the importance of documenting specific information such as indication, dosage form, dosage, off label medication, weight and height, etc. The ICSR should also provide information such as clinical symptomatology, physical findings, medical history, social factors, psychological issues, developmental problems, previous drug reactions, etc. In essence, a paediatric specialist should be available to provide a full work up of the child in order to contribute to a meaningful database that can be accessed for future use. The immediate concern would be in reference to low dosage preparations (off-label as well) in which clinical side effects might not be so apparent and therapeutic effectiveness may be minimal and difficult to assess. Proposed change (if any):	
Lines 275-299		Comment: P.IV.B.3. Periodic safety update reports (PSUR) This section details the importance of periodic safety update reports (PSUR) that document the risk-benefit ratio of various medication used in the paediatric population as an important tool to collect and analyze information. Furthermore, such reports should be used to assess effects of medications with specific indications as well as those without specific indications but perhaps used in in clinically less defined conditions. Such data will allow for more specific dosing, clearer indications, and an overall more accurate and effective approach to prescribing medications in the paediatric population across all age groups. Proposed change (if any):	

Lines 300-338		Comment: P.IV.B.4. Post-authorization safety studies (PASS) This section describes studies (PASS) that are conducted in the paediatric population to complement research which has already been performed and which can fill any possible gaps in knowledge. Such information can come from clinical practice documenting the paediatric groups treated as well as outcomes of treatment and create a good picture of daily use of the medication. Once again the overall aim should be to create a large database in order to follow paediatric patients in the long run as well as accumulate data on adverse effects of various medications administered across the paediatric age groups. Proposed change (if any):	
Lines 339-384		Comment: P.IV.B.5. Signal management Information obtained from observations in the paediatric population both adverse and beneficial are defined as signals. Once again it must be continually emphasized that such signals will clearly differ among various sections of the paediatric population based on age and degree of maturation; thus, must be placed in the proper clinical context. (age-specific) Reporting and recording of adverse reactions or signals will provide a certain amount of predictive ability to determine what populations might be at increased risk of developing adverse reactions as well as take necessary preventive measures such as modifying dosing, clinical indications, or closely monitor patients that might be at increase risk of developing adverse reactions.	
Lines 385-417		Comment: P.IV.B.6. Safety communication This section emphasizes the importance of communication with children and adolescents for them to be actively involved in the decision-making process concerning their health. Of	

Line 418-502		course, the approach taken by adults is of uttermost importance as will differ between young children and older adolescents. The importance of conceptualizing complex information understandable across various ages while still respecting the child's autonomy in the decision making process is of utmost importance. The avoidance of paternalism is important and a joint decision model should be followed seeking the overall best interest of the child in terms of health and well-being. Such therapeutic alliance should be formed between paediatric specialists experienced with particular aspects related to the individual cases, children, and their parents. Thus, consensus should be sought among all involved. Proposed change (if any): P.IV.C Operation of the EU network P.IV.C.1. Roles and responsibilities P.IV.B.6.2 European Medicines Agency PiV.C.2. Safety communication in the EU No comments or changes to add to the remainder of the document on any of these sections.	

Please add more rows if needed.

9 OCT 2017

Submission of comments on GVP Product- or Population-Specific Considerations IV: Paediatric population (EMA/572054/2016)

Comments from:

Name of organisation or individual
EUCROF (EU CRO Federation), PharmacoVigilance Working Group and Late Phase Working Group

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received (please see privacy statements: http://www.ema.europa.eu/ema/index.jsp?curl=pages/home/general/general_content_000516.jsp&mid *and* http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123144.pdf*).*

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF) (see Introductory cover note for the public consultation of GVP under Practical advice for the public consultation: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123145.pdf*)*
.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	EUCROF applauds the Agency's initiative to provide support to the industry in the interpretation of pharmacovigilance legislation and guidance. This GVP document is well written and provides an interesting overview of considerations in paediatric populations. However, EUCROF considers that the industry may have challenges understanding and implementing items that impact daily operational activities. This document contains information that is largely duplicative of other GVP modules, with only a small amount of information that has additional operational impact. EUCROF is concerned that industry representatives may not be aware that multiple documents have to be consulted to identify all requirements relating to a particular activity, e.g. for signal detection activities this document has to be consulted in addition to GVP Module IX. EUCROF's preferred approach would be to combine this information into the core GVP modules to avoid creating multiple documents requiring review by operational staff. However, assuming the Agency is committed to publishing this as a separate document, EUCROF would encourage adding cross-references to this document in all impacted core GVP modules to ensure that readers of	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	those modules do not miss additional requirements contained within this document.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Line 134		Comment: In current version of Annex 1, medication error is not defined separately but incorporated into the definition for an ADR. Thus, the reference to Annex 1 may be confusing. However, medication error is separately defined in Module VI Rev2. Proposed change (if any): (See GVP Module VI Rev2)	
Footnote 11 page 5		Comment: Link doesn't work. Update the link Proposed change (if any):	
Lines 141-142		Comment: The lack of development of medicines for paediatric patients and of paediatric dosing guidance in the product information is leading more to intentional off-label use and misuse than to unintentional medication errors Proposed change (if any): Historically there has been a lack of development of medicines for paediatric patients and of paediatric dosing guidance in the product information, leading to off-label use and misuse.	
Lines 212-232		Comment: According to GVP Module VI revision 2, "reporting" is now substituted by the term "submission" when reporting adverse events to regulatory agencies. Thus, using the term reporting is inconsistent with the associated GVP module.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		Proposed change (if any): Change the term Reporting for Submission where appropriate	
Lines 230-232		Comment: *"Appropriate **skills** to address the aspects specific to this population"*: The current wording is open to interpretation and could be taken to imply that each company would require a paediatrician to perform these activities. The majority of marketing authorisation holders will not have the resource to employ a paediatrician, or the need to employ one unless their product portfolio has significantly represented in the paediatric population. SMEs and organisations that have minor representation in paediatric populations would need to be aware of these requirements, but would not need a paediatrician on staff. Proposed change (if any): Appropriate training to address the aspects specific to this population.	
Section P.IV.B.4. Post-authorisation safety studies (PASS)		General comments from LP Working Group about this section: Lines 301-302 state that "*The requirements for the design and conduct of post-authorisation safety studies (PASS) in GVP Module VIII should be followed*". However, Module VIII is strictly related with GVP Annex I (Definitions) where a NIS is defined as a study in which "*the medicinal product is prescribed in the usual manner in accordance with the terms of the marketing authorization*". This definition is quite controversial: it was and still it is object of discussion among methodologists (see for example: ENCEPP considerations on the definition of NIS [http://www.encepp.eu/structure/documents/ENCePPconsiderationsNIS.pdf] where (in pages 4 and 5) it is stated that "*registries in which the data collected derive from routine*	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		clinical care" and prospective "*studies which evaluate patterns of the usage of medicines, including potential off-label use …" should "… never be considered as falling within the scope of Directive 2001/20/EC"*, thus should be considered NIS). In lines 306-308 it is also stated that "*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 …*". In lines 150-151 it is also reported that "*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*". Based on all these considerations, EUCROF LP WG is worried that a rigid interpretation of the GVP Annex I definition of NIS could move a PASS (e.g. a Drug Utilization Study or a Registry) designed according with observational methods in the field of Clinical Trials discouraging the conduction of NIS to evaluate in the real life the phenomenon of the off label use in the paediatric populations where, according with data from literature, it's unfortunately frequent. Proposed change (if any):	
Line 339		Comment: EUCROF notes that the consultation for the next version GVP Module IX includes a cross-reference to this new paediatric guideline. EUCROF encourages that this cross-reference is maintained as GVP Module IX is finalised. Proposed change (if any):	
Line 385		Comment: Similarly, EUCROF encourages that cross references to this guideline in Module XV and XVI are maintained.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		Proposed change (if any):	
Line 441		Comment: Ensure that a cross reference to this guideline in Module VII is maintained. Proposed change (if any):	
Lines 378-380		Comment: In order to introduce flexibility in case of drugs that are not focused on paediatric indications or do not have large volume of paediatric cases, we would recommend to use the verb “may” instead of “should” in the sentence: *“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.”* Proposed change (if any): Considering that the nature and/or severity of adverse reactions in paediatric patients may depend on organ maturation stage, any signal detection methods **may** focus not only on the paediatric population as a whole, but also on specific paediatric subpopulations.	

END of document

13 October 2017

Submission of comments on GVP Product- or Population-Specific Considerations IV: Paediatric population (EMA/572054/2016)

Comments from:

Name of organisation or individual
Medicines for Europe

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received (please see privacy statements: http://www.ema.europa.eu/ema/index.jsp?curl=pages/home/general/general_content_000516.jsp&mid *and* http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123144.pdf*).*

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF) (see Introductory cover note for the public consultation of GVP under Practical advice for the public consultation: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123145.pdf*)*
.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	Medicines for Europe, representing generic, biosimilar and value added medicines industry, welcomes the newly drafted GVP Module focusing on the paediatric population. Child age-specific information on efficacy and risk of medicines can be limited for healthcare professionals and patients. It is therefore very important to make the best use of a risk planned approach to the pharmacological treatment of children. This means pharmacovigilance in the broadest sense of gaining the best data from the use of medicines in clinical practice. We welcome the fact that the importance of performing specific research in pharmacovigilance targeting the paediatric population has been recognised and established. Especially bearing in mind that systematic issues as medication errors, off-label use and the lack of age-suitable formulations are considerable obstacles for same medication use in paediatrics.	
	The consulted GVP module is in our opinion sufficiently addressing all key areas, is well structured and overall clearly written. In the specific comments section we listed some of our proposals we believe might contribute additionally to the clarity and avoid any unnecessary misinterpretation.	
	Additionally, we would like to draw your attention to the reference made to the GVP Module V. Specifically, part P.IV.B.1 Risk Management Plan of this draft guidance is referring to GVP Module V and its considerations applicable for paediatric population. However, this draft guidance is referring mainly to potential risks and their management when product is indicated in the paediatric population(s). Please note that for the majority of the new products paediatric population will be listed under missing information, which should be also in our opinion be addressed in this guidance. Especially since the GVP V Rev 2 does no longer explicitly list paediatric population (compared to	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	the previous version) among examples to be addressed in the V.B.5.5. RMP part II, module SIV “Populations not studied in clinical trials”.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
124-126		Comment: The sentence should be refined and clarified. Proposed change (if any): This has also an impact on the potential of clinical trials to ~~gather~~ *generate* sufficient ~~numbers~~ *sample size* *to evaluate safety issues* ~~for generating dedicated~~ *and gather* information on incidence of adverse reactions in the same fashion of adult clinical trials.	
130-131		Comment: The sentence should be refined and clarified. Proposed change (if any): Furthermore, ~~the size of the paediatric safety database available for a given medicine in comparison to what is available for adults~~ *databases for safety evaluation in the paediatric population for a given medicine* can be scarce or a paediatric safety database may not even be available	
178-180		Comment: Please clarify 'some approaches' or provide a more specific wording. Alternatively providing some examples might contribute to more clarity. Proposed change (if any): -	
204		Comment: Editorial proposal.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		Proposed change (if any): or ~~to include~~ inclusion of paediatric subjects	
204-205		Comment: Relying on extrapolation of an adult is true for many products that are not indicated for the paediatric population. We would recommend Proposed change (if any): ….. may be of particular value when *the all the below points apply;*	
206-208		Comment: The point is well taken. However, this might be true for many (or even for all products) that are not indicated for the paediatric population. Proposed change (if any): -	
242		Comment: P.IV.A only refers to four groups, correction is needed to align information. Proposed change (if any): correct P.IV.A or line 242	
257		Comment: Please consider including also gender and ethnicity. Proposed change (if any): -	

Please add more rows if needed.

<12 October 2017>

Submission of comments on GVP Product- or Population-Specific Considerations IV: Paediatric population (EMA/572054/2016)

Comments from:

Name of organisation or individual
PIERRE FABRE

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received (please see privacy statements: http://www.ema.europa.eu/ema/index.jsp?curl=pages/home/general/general_content_000516.jsp&mid *and* http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123144.pdf*).*

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF) (see Introductory cover note for the public consultation of GVP under Practical advice for the public consultation: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123145.pdf*)*
.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Lines 364-369 and lines 375-377		Comment: Sub-Group analysis with stratification by age and comparison of disproportionality analysis is a recommendation or requirement to be performed routinely in signal management for Pediatric indications? Proposed change (if any):	
		Comment: Proposed change (if any):	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 October 2017

Submission of comments on GVP Product- or Population-Specific Considerations IV: Paediatric population (EMA/572054/2016)

Comments from:

Name of organisation or individual
Royal College of Physicians - Joint Specialty Committee for Clinical Pharmacology and Therapeutics

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received (please see privacy statements: http://www.ema.europa.eu/ema/index.jsp?curl=pages/home/general/general_content_000516.jsp&mid *and* http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123144.pdf*).*

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF) (see Introductory cover note for the public consultation of GVP under Practical advice for the public consultation: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123145.pdf*)*
.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	It is not clear how older children or younger teens could be encouraged to report adverse reactions. These patients may not mention problems to their parents. It would seem to be good practice to devise specific methods of capturing the voice of these patients if they experience adverse effects.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		Comment: Proposed change (if any):	

Please add more rows if needed.

<Date of submission>

Submission of comments on GVP Product- or Population-Specific Considerations IV: Paediatric population (EMA/572054/2016)

Comments from: Sue Jordan

Name of organisation or individual

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received (please see privacy statements: http://www.ema.europa.eu/ema/index.jsp?curl=pages/home/general/general_content_000516.jsp&mid *and* http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123144.pdf*).*

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF) (see Introductory cover note for the public consultation of GVP under Practical advice for the public consultation: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123145.pdf).

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	Thank you for the invitation to comment on this important document.	
	Line 88. Some mention of exposure *via* breast-milk is needed to complete the categorisation. There are particular concerns over premature infants.	
	Lines 111-3. Would it be worthwhile to include the example of SSRI use in adolescents? Hetr ick SE, McKenzie JE, Cox GR, Simmons MB, Mer ry SN. Newer generation antidepre ssants for depressive disorders in children and adolescents. Cochrane Database of Systematic Reviews 2012, Issue 11. Art. No.: CD004851. DOI: 10.1002/14651858.CD004851.pub3.	
	Line 141. I agree that lack of guidance and information would lead to errors, but these would be most likely to be confined to certain error categories, such as inappropriate prescribing, and failure to monitor medication.	
	PIV.A.1.5 lines 163-170. These statements indicating that a systematic approach is needed to check patients for potential adverse effects are very welcome.	
	1.Line 209. I agree with this suggestion that long-	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	term follow up should be mandated to ensure patient safey. This can be achieved in countries with electronic population coverage, for example, Scandinavia, Wales, and should be integral to the funding of paediatric trials, for example Davies G, Jordan S, Brooks CJ, et al. Long term extension of a randomised controlled trial of probiotics using electronic health records. Sci Rep. 2018 May 16;8(1):7668. doi: 10.1038/s41598-018-25954-z. https://rdcu.be/OorT	
	l.216. I suggest it should be noted that spontaneous reports only capture 5% of adverse events, reporting is biased and not amenable to educational interventions. Suggested text: We acknowledge the limitations of spontaneous reporting: some 5% of serious ADRs are reported via spontaneous reporting systems, such as the iconic 'yellow card' scheme (Hazell & Shakir 2006); increased reporting induced by intensive training is not sustained (Lopez-Gonzalez et al 2015). Reliance on volunteer reporting renders spontaneous reporting systems vulnerable to respondent and notoriety biases (Pariente et al 2007, de Boissieu et al 2014). However, without the development of databases capturing the full spectrum of adverse events, from falls to failure to thrive, spontaneous	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	reporting remains important, and strategies to promote compliance are needed. Hazell, L. and S.A. Shakir, *Under-reporting of adverse drug reactions : a systematic review.* Drug Saf, 2006. **29**(5): p. 385-96. Lopez-Gonzalez, E., et al., *Effect of an educational intervention to improve adverse drug reaction reporting in physicians: a cluster randomized controlled trial.* Drug Saf, 2015. **38**(2): p. 189-96. Pariente, A., et al., *Impact of safety alerts on measures of disproportionality in spontaneous reporting databases: the notoriety bias.* Drug Saf, 2007. **30**(10): p. 891-8. de Boissieu, P., et al., *Notoriety bias in a database of spontaneous reports: the example of osteonecrosis of the jaw under bisphosphonate therapy in the French national pharmacovigilance database.* Pharmacoepidemiol Drug Saf, 2014. **23**(9): p. 989-92. Background: Our group is working on systematic reporting of adverse events via dedicated *pro formata*, including in adolescent services, for information see http://www.swansea.ac.uk/adre/. This approach is effective in reducing prescribing of mental health medicines.	
	l.259. Would it be useful to ascertain, with a specific question, whether any preparations were crushed or split? There is a risk that this information would not otherwise be reported.	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	Line 278. ‘risk-harm’ balance I suggest that the term benefit-harm balance is preferred over benefit-risk balance: risk implies a probability, whereas both benefit and harm are actual outcomes.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
45		Comment: the indefinite article should be deleted Proposed change (if any): need scientific	
276		Comment: preposition required Proposed change (if any): included in	
314-5		Comment: meaning unclear, perhaps incorrect noun Proposed change (if any): Ethical and feasibility issues may compromise the conduct of PASS.	
318		Incorrect preposition. But because the inclusion …. Long sentence. Suggest split the sentence.	
322-5		Sentence too long. Meaning not clear. … allowing researchers to address …	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<13 October 2017>

Submission of comments on GVP Product- or Population-Specific Considerations IV: Paediatric population (EMA/572054/2016)

Comments from:

Name of organisation or individual
SIOPE – European Society for Paediatric Oncology based on input from: - [redacted] Pharmacovigilance Unit, Gustave Roussy Comprehensive Cancer Center, Villejuif, France

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received (please see privacy statements: http://www.ema.europa.eu/ema/index.jsp?curl=pages/home/general/general_content_000516.jsp&mid *and* http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123144.pdf*).*

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF) (see Introductory cover note for the public consultation of GVP under Practical advice for the public consultation: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123145.pdf*)*
.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	Overall, SIOPE acknowledges the relevance of a paediatric pharmacovigilance guideline and supports the document prepared by the European Medicine Agency (EMA). There is a crucial need to improve the current situation since pharmacovigilance in the paediatric population is not performing well and not addressing the goals and challenges at a time when many new medicines are evaluated and/or prescribed off-label. SIOPE believes that it is of the utmost importance to get health care professionals and parents educated and more committed and to develop innovative proactive programmes, in particular in the field of off-label use, beyond spontaneous declaration. More specifically, the Guideline may gain from more clarity as to its specific scope: is it only about pharmacovigilance of medicinal products used in the paediatric population after a marketing authorisation (which seems to be the case) - or also applies to clinical trial settings?	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	Further, the target audience to whom the document is addressed should be widened – at present, it only encompasses Marketing Authorisation Holders (MAHs), national competent authorities and the EMA. Parents, patients, patient organisations, healthcare professionals, organisations of national healthcare systems (e.g. regional centres of pharmacovigilance in France) and learned societies/paediatric research networks can and should play an important role in the reporting of side effects, education, and signal detection. It is of vital importance that these roles are acknowledged and that these stakeholders are specifically addressed by the document as well. While of a major importance, risk minimisation measures only have limited scope in the document (with several mentions in the section on Safety Communication, which is not most appropriate for this topic). Furthermore, evaluation of the effectiveness of risk minimisation measures should be mentioned. The emphasis is still put on spontaneous notification, whereas this system has shown its limits. Proactive surveillance systems can be further highlighted that may encompass: registry, observational study with real-life safety data, post-authorisation safety study….	

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*
	Periodic benefit-risk evaluation report (PBRER) is not mentioned in this GPV guideline (ICH guideline E2C (R2). Although new Pharmacovigilance legislation (Regulation (EU) No 1235/2010 and Directive 2010/84/EU) introduced changes that are particularly relevant for the paediatric population - in particular, an extended definition of adverse reaction which includes harm resulting from over- or under-dosing (due to lack of age-appropriate formulations), misuse, and abuse - these topics are not addressed in the present document. Other important sources of safety data and topics not mentioned/addressed: published literature, meta-analysis of clinical trials, epidemiologic data.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
P.IV.B.4. Post-authorisation safety studies (PASS) **(Lines 300-338)**		Comment: PASSs can also include clinical trials, not only non-interventional studies. MAHs are obliged to carry out imposed PASSs but why only MAHs are cited as able to conduct voluntary PASSs (in GVP module VIII)? Proposed change (if any): Specify that voluntary PASSs can be conducted by academic sponsors, and not only by MAHs. Specify if the sponsor can still seek scientific advice (for the protocol) from the EMA Pharmacovigilance Risk Assessment Committee.	
P.IV.B.6. Safety communication **(Lines 385-417)**		Comment: There is an apparent confusion in this chapter between risk minimisation measures and communication to the general public and health care professionals. Proposed change (if any): these two issues should be presented and discussed separately.	
P.IV.C.1. Roles & responsibilities **(Lines 419-465)**		Comment: Parents, patients and their organisations as well as healthcare professionals and learned societies/paediatric networks in their active role are largely out of scope in this section (and indeed the consultation document as a whole). Proposed change (if any): The above stakeholders should be added/specified as the intended addressees of the document.	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 Oct 2017

Submission of comments on GVP Product- or Population-Specific Considerations IV: Paediatric population (EMA/572054/2016)

Comments from:

Name of organisation or individual
UCB BioPharma

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received (please see privacy statements: http://www.ema.europa.eu/ema/index.jsp?curl=pages/home/general/general_content_000516.jsp&mid *and* http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123144.pdf*).*

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF) (see Introductory cover note for the public consultation of GVP under Practical advice for the public consultation: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123145.pdf*)*
.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment	Outcome *(To be completed by the Agency)*

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Line 93		Comment: Consideration should be given to expanding “Paediatric subjects differ substantially from adults due to the ongoing neurobehavioural development and physical growth, including internal organ maturation.” to include additional considerations. Proposed change (if any): “Paediatric subjects differ substantially from adults due to the ongoing neurobehavioural development and physical growth, including internal organ maturation. This also includes psychological development and their ability to express symptoms, especially at an earlier age.”	
Line 101		Comment: Consideration should be given to expanding the text to add physiological parameters and differences between different age groups and adults. Proposed change (if any): “• 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), changes in the physiological parameters during growth and their development (ontogeny), differences in these between the different age	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		groups and adults leading to a different pharmacodynamic and pharmacokinetic profile of a medicine as known in adults;"	
Line 114		Comment: Consideration should be given to expanding the text to add developmental physiological. Proposed change (if any): "These considerations highlight the importance of taking into account aspects related to organ maturation, developmental physiology and developmental pharmacology when performing pharmacovigilance activities for the paediatric population…"	
Line 176		Comment: Consideration should be given to expanding the text to consider preclinical data. Proposed change (if any): "In general, the knowledge gained from the adult population – when available - and those from preclinical data should inform best use of data collection methods and risk minimisation tools when approaching risk management for paediatric subjects."	
Line 290		Comment: Consideration should be given to expanding the text to add exposure of patients by age group.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		Proposed change (if any): "Furthermore, information on: • the number of paediatric patients exposed during the reporting period, the exposure of patients by age group and the method of exposure calculation; …"	

Please add more rows if needed.