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 – Sini Eskola (sini.eskola@efpia.eu) |

*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 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.  |  |

1. 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; 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): 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 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 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 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*,” 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.  **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.**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.**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:**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 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 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-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. **Proposed change:**Additional clarification is required. |  |
| Line 318 |  | Delete the word ‘of’ in the following clause: “…but because of 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. |  |
| 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 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 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 adultsComment: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 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 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 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 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…*” |  |
| 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.