European Medicines Agency
Post-authorisation Evaluation of Medicines for Human Use

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OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON CONDUCT OF PHARMACOVIGILANCE FOR MEDICINES USED BY THE PAEDIATRIC POPULATION

Table 1: Organisations that commented on the draft Guideline as released for consultation

	Name of Organisation or individual	Country/Head Office
1	Association Européenne des Spécialités Pharmaceutiques Grand Public (AESGP)	BELGIUM
2	CPS Research	UNITED KINGDOM
3	Drug Safety Research Unit (DSRU)	UNITED KINGDOM
4	European Federation of Allergy and Airway Diseases Patients'Association (EFA)	BELGIUM
5	European Federation of Pharmaceutical Industries (EFPIA)	GERMANY
6	European Society for Developmental, perinatal and Paediatric Pharmacology (ESDP)	UNITED KINGDOM
7	International Plasma Fractionation Association (IPFA)	NETHERLANDS
8	International Primary Care Respiratory Group (IPCRG)	UNITED KINGDOM
9	Medicines Evaluation Board (MEB)	NETHERLANDS
10	Neonatal & Paediatric Pharmacist's Group (NPPG)	UNITED KINGDOM
11	Novartis Pharmaceuticals Corporation	USA
12	Task-force in Europe for Drug Development in the Young (TEDDY)	ITALY
13	UK Clinical Research Network Co-ordinating Centre (UKCRN)	UNITED KINGDOM

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Table 2: Discussion of comments

GENERAL COMMENTS - OVERVIEW
The general comments received about the draft guideline were positive ("the document is sensible and encompasses the important areas in terms of improving pharmacovigilance in paediatrics", "the document is extremely well thought and written and we fully agree on its content and recommendations", "EMEA has issued basic recommendations ...[that] …advances a common standard in drug safety for children", "we would like to firstly fully support the thrust and importance of these proposals"). The main reservations expressed were that "much of the guideline refers to new or evolving concepts with which there is limited experience… [and] ..."the document is limited in its provision of details that pharmaceutical firms can use in routine pharmacovigilance planning". The specific difficulties of monitoring Pharmacovigilance in off-label use were highlighted and clarifications about the role and responsibilities of pharmaceutical companies regarding the implementation of the Guideline were considered important. Comments applying to specific parts of the text of the draft guideline are summarised in the table below.

SPECIFIC COMMENTS ON TEXT

1. INTRODUCTION

Line no. + para no.	**Comment and Rationale**	**Outcome**
	The need for the revision of the guideline when the regulation on medicinal products for paediatric use is finalised should be added.	Comment taken into account. The guideline has been updated with the references and the day of entry into force of the paediatric regulation.

2. BACKGROUND

Line no. + para no.	**Comment and Rationale**	**Outcome**
1st paragraph, 1st sentence	"The paediatric population is defined…as those between 0 and 18 years". Explicit mention that premature babies are included in the scope of this guideline but that embryo/foetus are excluded (as "bystander or patient") is requested.	Incorporated.

1st paragraph	In addition, the efficacy of a drug can be very different in children than in adults, as childhood diseases and disorders may be qualitatively and quantitatively different from their adult equivalents. This may result in a different benefit-risk balance.	This comment has been taken into account in section 4, where it is better placed.
3. CONSIDERATION OF DIFFERENT PRODUCT TYPES		
Line no. + para no.	**Comment and Rationale**	**Outcome**
2nd paragraph, 3rd sentence	The need for database, and the optimal cost/effectiveness ratio, is emphasised. It is considered that it would be even better to use non disease oriented database.	No substantial changes to the text are needed.
2nd paragraph, last sentence	Specialist networks, primarily paediatricians' networks, would add to the clinical value and validity of the collected information.	Comment taken into account. Importance of networks emphasised by editorial change (section 6.1 of the final version)
4. THE ROLE AND RESPONSIBILITIES OF DIFFERENT STAKEHOLDERS		
Line no. + para no.	**Comment and Rationale**	**Outcome**
1st sentence	Patient organisations, as representatives of patients, should not be forgotten.	Incorporated.
1st sentence	National health systems should be added	Incorporated.
2nd sentence	It is critical for the EMEA to repeatedly communicate the contribution that health care practitioners can make to the process by reporting ADRs.	Incorporated.
2nd sentence	The need for participation by parents and caregivers must be stressed with educational messages directly targeted toward them. Their co-operation is integral to securing long-term follow-up on adverse reactions that may become only apparent after months or years.	Incorporated.
2nd sentence	A process should be required to ensure that all stakeholders are genuinely included in the process of pharmacovigilance.	Noted, but not incorporated as it is outside the legal provisions of the current legislation. General requirements for Pharmacovigilance and ADR reporting are described in Vol 9 A of the Rules governing medicinal products in the European Union.

2nd sentence	Clarification about role and responsibilities of pharmaceutical companies regarding the implementation of the Guideline was considered important. Specific clarification about responsibilities were requested in long term pharmacovigilance i.e. the maintenance of registries and follow-up that continues beyond the patent expiry as well as regarding the generic manufacturers responsibilities.	Noted, but not incorporated. Long term pharmacovigilance commitments may be part of a paediatric investigation plan or part of the condition of a marketing authorisation. It would not be appropriate for this guideline to pre-empt either of those situations or to encroach on primary legislation.
	This section is very vague and a thoughtful recognition of the proper roles of stakeholders is key. Stakeholders should determine what data elements need to be reported, who should do it, how to encourage ADR reporting by health care practitioners and patients and how to communicate new paediatric safety information to the public.	Section expanded to take comments into account.

5. SPECIAL CHARACTERISTICS OF PAEDIATRIC PHARMACOVIGILANCE

Line no. + para no.	Comment and Rationale	Outcome
1st paragraph, 3rd sentence	This is especially true for CNS effect should be added after the third sentence.	Incorporated.
1st paragraph, last sentence	It may be not only the rapid changes in body mass, but also changes in morphology and body composition that play a role.	Incorporated.
1st paragraph	In addition, the efficacy of a drug can be very different in children than in adults, as childhood diseases and disorders may be qualitatively and quantitatively different from their adult equivalents. This may result in a different benefit-risk balance.	Incorporated.
2nd paragraph	This raises the need for further research.	Noted. Not deemed necessary to be included in the guideline.
2nd paragraph	Suggested new paragraph Treatment in childhood may also result in ADRs occurring in later life. Also in case of life-long treatments for chronic diseases, the total duration of treatment is longer if started in childhood, which may expose the patient to additional risks (e.g. cancer, tooth decay due to drugs causing dry mouth, osteoporosis due to antiepileptic drugs etc)	The first sentence was already in the draft. The second sentence has been incorporated

2nd paragraph	Suggestion of adding a new bullet point o Significant ADRs in children appear to be less common in the community than in the hospital	Not incorporated. This bullet point is not relevant to the section.
3rd paragraph, 1st sentence	Add “airways and skin” alongside “kidney, liver, blood brain-barrier”	Incorporated.
3rd paragraph 1st bullet point	Particular concern was expressed regarding pharmacokinetics and dose ranging studies taking in account drug absorption from the skin, lung and the nose. In some instances inhaled asthma medications have been associated with much higher side-effects than would be expected in adults. The small number of thorough dose-ranging studies in children for these products is surprising.	The guideline refers to the need for paediatric PK studies and dose-finding studies.
3rd paragraph, 1st bullet point	It is possible to collect routine data and samples to investigate whether, and to which extent, the pharmacokinetics and pharmacodynamics of a compound is different in the paediatric population however it is necessary for the EMEA and national governments to set up such systems.	Not incorporated. Not relevant for this guideline focusing on pharmacovigilance aspects.
3rd paragraph, 2nd bullet point	There is very little information on the safety and acceptability of excipients. It is proposed that EMEA conduct a systematic review in conjunction with pharmaceutical industry on the above aspects. The results should be public.	Not incorporated. Not relevant for a guideline.
3rd paragraph, 4th bullet point	Long-term follow-up data may be necessary to detect delayed ADRs. However it is no longer affordable or sensible to collect data until a long-term or growth ADR is suspected. It is paramount to make use of suitable networks and databases or record linkage systems which collect the appropriate routine information.	Not incorporated. There are many ways of exploring delayed ADRs. All options are to be kept open.
3rd paragraph, 5th bullet point	The hypothesis of drug-induced “programming” has not been widely studied. Perhaps the EMEA might refer this matter to the EU Commission suggesting it as a topic on which to promote further investigation.	Not incorporated. Not relevant for a guideline.
3rd paragraph, 6th bullet point	It is proven that some ADRs may only occur in the paediatric population – see Reye syndrome	Point already made. Examples are not being given routinely in this section of the guideline.
4th paragraph,	Suggestion to change the beginning of the first sentence to “The	Not incorporated. Original text preferred.

1st line	problems may be accentuated…"	
4th paragraph, 2nd bullet point	Legal and liability aspects need to be considered in the under-reporting of ADRs in off label use.	Incorporated
4th paragraph, 2nd bullet point	Suggestion to change to o Undereporting of adverse drug reactions may occur in relation to unlicensed or "off-label" use	Incorporated.
6th paragraph	Premature babies are certainly a distinct group but special attention should also be given to newborns, infants and elder children of pre-scholar age because of biological, developmental and communication characteristics.	Not incorporated. The point of mentioning premature infants is that they are at higher risk. Although the other categories mentioned in the comment have specific characteristics they are not at a higher risk than premature infants.
6. CLINICAL SAFETY AND PHARMACOVIGILANCE BEFORE AUTHORISATION OF A PAEDIATRIC INDICATION		
Line no. + para no.	**Comment and Rationale**	**Outcome**
General	Pre-licensing studies and developing the summary of characteristics before the drug goes on the market, why is more specific advice not given regarding what is put in the SPC? When a drug is indicated in "children" it needs to be specific and mention the age range at which it can be used and not use a non-specific term such as "children".	Not incorporated. This guidance is set out in the EU Guideline on the summary of product characteristics, Revision 1, October 2005.
1st paragraph, 4th sentence, line 6 to 8	Clarifications are needed. This sentence seems to refer to cases where no information is available to suggest that there is a theoretical possibility for a serious adverse event to develop after a latent period or is triggered by a change in growth or development. It would be helpful to give an example of such a serious and rare event and to clarify how it has been determined that it was associated with the use of drug. If the statement refers to cases where there is information to suggest that there is possibility for a serious adverse event to develop after a latent period before onset or it can be triggered by e.g. a change in growth or development it would be helpful to make this clear.	The statement refers to either case. Both comments not incorporated. The guideline does not give examples.
1st paragraph,	The recommendation that "*Should an ADR occur a blood sample should be taken, if possible, and frozen for drug and metabolite*	Comments taken in account. Wording clarified to indicate that this should take place within the context of a clinical trial programme, and details

last line	*measurement"* has raised numerous comments expressing concerns about: -the additional implications including cost (especially for trials not sponsored by pharmaceutical companies), -the need to mention the possibility of blood sampling in the event of ADR in the protocol for clinical trial as well as in the inform consent form and the possible under-reporting of non serious ADRs by parents/children in order to avoid it, Clarifications were especially requested regarding: -the categories of ADRs for which it should be done -the timing of such collection -the parties responsible to decide when such further testing is needed and to collect and store the blood samples -the need of informed consent in non interventional study or off label use when it is not considered of direct benefit to the patient	should be set out in the clinical trial protocol. Example now given is that of taking blood following a serious ADR. This could not occur within the context of a non-interventional study, by definition.
2nd paragraph	These statements are crucial and indicate a very important direction. The EMEA should require that the paediatric investigation plan presented for every old and new drug (with some reasonable exceptions) for which the authorisation of a paediatric indication is requested, includes the plan for long-term post-authorisation studies, at least partially funded by the pharmaceutical company.	Not incorporated. Not considered relevant for this guideline, as it is more appropriate for the PIP content.
2nd paragraph, 1st line	(i.e. safety has not been demonstrated) should be deleted	No rationale given for this. Not incorporated.
3rd paragraph, 2nd sentence	Cross reference to relevant ICH guidelines should be provided in order to clarify under which circumstances juvenile animal studies should be considered (i.e. ICH M3 - section 11, ICH E11 – section 2.1, ICH S 5A, note 17)	Incorporated.
4th paragraph	Clarifications/advices were requested about -the collection and storage of blood and saliva samples -the need of informed consent in non interventional study or off label	 Incorporated. Blood and saliva samples cannot be collected, by definition, in a non-

	use when it is not considered of direct benefit to the patient.	interventional study.
4th paragraph	A specific paediatric example should be proposed if possible.	The guideline does not include examples.
5th paragraph, 1st line	"to" should be added in "Whenever a medicinal product is likely [to] be used in the paediatric population…",	Incorporated.
5th paragraph, 2nd sentence	The "paediatric plan" that should be included in the Pharmacovigilance Plan (PP) could be confused with the "Paediatric Investigation Plan" and the term is proposed to be changed in "paediatric section".	Incorporated.
	For clinical trials in children it may be worthwhile to expand the definition of expeditable reporting to certain events depending on the type of clinical trial	Not incorporated. Firstly, it would be confusing to have different definitions of expedited reporting for different age groups. Secondly, this is outside current legal provisions.
	Clarifications were requested regarding the reporting requirements of organisations involved in clinical trials without collaborating with MA holders (reporting to MAHs as well as to competent authority?)	Not incorporated. Reporting requirements in clinical trials are set out in the clinical trials directive and its implementing texts.
	The suggestions for prospective monitoring are welcome but a number of principles ought to be outlined which are currently not made entirely clear: All surveillance programmes should include a fully independent data monitoring committee and that all data should be made publicly available Appropriate control populations are identified for valid comparisons to minimise reporting bias Plans should allows recording of off-label use Plans should include methodology to ensure that data are representative of use and not just include reports from highly motivated clinicians or patients	Not incorporated. This is too broad a requirement and cannot be mandated in a guideline. These comments are more appropriate for the next section. Mentioned in the next section. This is not specific to paediatric pharmacovigilance.

7. PHARMACOVIGILANCE FOR PRODUCTS ON THE MARKET (INCLUDING "OFF-LABEL" USE)		
Line no. + para no.	**Comment and Rationale**	**Outcome**

General		
	Even in the best clinical development programmes, there is an under-representation of children and so there will be limited information on the use of medicines in children at the time of marketing the medicines. As noted in the draft guidance there is a range of different age groups of children and clinical trials are unlikely to cover all age ranges adequately; so monitoring the use of medicines in children during the post-marketing phase is very important.	This point is made in the guideline. Incorporated.
7.1 Data collection		
Sponta-neous reports		
1st paragraph, penultimate sentence	Add "possible" before reluctance	Not incorporated. Prefer original text.
1st paragraph, last sentence	Although it is agreed that MAH and competent authorities should encourage ADR reporting both in licensed and off label use, the difficulties are highlighted especially regarding the possible liability issues for the health care professional. It is considered as useful for the Agency to provide detailed information on how reporters and their ADRs reports will be protected from exposure to external parties such as attorneys leading class action lawsuits. If feasible under EU legislation, a mechanism to preserve their identities should be made available. If legally feasible under EU law, the EMEA could encourage health professionals to have the confidence to self report in the knowledge that the information will be reviewed with a no blame approach, for example, through the anonymity of professional societies and local paediatric groups. Confidential submission should be encouraged in such cases to maximise data collection.	Noted. This is not specific to paediatric pharmacovigilance. The need for reassurance on confidentiality has been incorporated. There is a problem in encouraging reporting through a professional society as this may make follow-up on reports more difficult. A better approach is to give reassurance on confidentiality, which is incorporated.

2nd paragraph	Recommendation to give a role to pharmacists in the reporting of ADRs	Pharmacists already have a role in reporting ADRs in a number of Member States. Specific mention incorporated.
2nd paragraph 1st sentence	Delete "Unless the reluctance to report can be overcome,"	Not incorporated. Original text preferred.
2nd paragraph, 3rd and 7th sentences	Encouraging families to report ADRs is considered worthwhile but concerns were expressed that such reports may not always be passed to regulatory bodies. A form alongside the patient leaflet may be helpful to encourage detailed recording and assist the physician in reporting.	In some Member States patients/carers can report directly to the regulatory authorities.
2nd paragraph	It would be important to revise this subsection in order to take in considerations the following issues and constraint: The quality of the information in the reports will be useless for analysis and future prescribing decisions if new data collection tools and systems are used inconsistently by different companies. If data reporting across compounds varies, comparisons of therapies will not be possible – one of the most critical component of an initiative to rationalise pharmacovigilance for medicines used by paediatric populations. Any change in the process of reporting of events in the paediatric population alone will also alter the dynamic between paediatric and adult reporting and so make any comparisons between the different populations difficult to interpret. The need for a specific form for paediatric ADR is questioned. The EMEA should take in consideration: the need to harmonise implementation through Member States and, ideally, across ICH regions, deviations to ICH E2B, the need for MAH to incorporate new data fields and form templates to their safety databases, the risk of error for reporters among different ADR forms especially if the age of the patient is initially unclear.	The first comment is true for all adverse event reporting. Reference to a specific form for a paediatric ADR has been deleted. Taken into account. Reference to a specific form for a paediatric ADR has been deleted.
3rd paragraph, 1st bullet point	The information being collected is adequate. Most reporters value and appreciate feedback about their report and this need of feedback needs to be emphasised with a separate bullet point. This feedback needs to be user friendly rather than an un-interpretable mass of paper sent to the reporter.	Incorporated.

4th paragraph, second and last sentence	Liability issues may not encourage reporting of ADRs resulting from medications errors.	Incorporated.
4th paragraph, last sentence	Add to the end "including details of the formulations involved with information on any manipulations needed to be made to the product by medical, nursing or pharmacy staff"	Incorporated.
Targeted Active data collection		
	Clarifications have been requested regarding the responsibilities for these activities: the MAHs, the national competent authorities, the EMEA, some other entity or partnership of these groups.	Incorporated.
	Primary care network as well as paediatric network should be mentioned. Combined data recording with primary and secondary care data linkage is considered important.	Incorporated.
	An appropriate control group should be considered in follow up evaluations. (NL)	Incorporated.
	Issues about consent and confidentiality merit consideration. Limiting data to consenting patients or parents may limit representativeness and should be unusual. Confidentiality should be explicit.	Statement on confidentiality incorporated.
	There is evidence in literature that patients are at least as efficient as doctors at recognising and attributing drug adverse events. Targeted active data collection is relevant to the collection of adverse events direct from parents. Research in developing techniques for direct patient communication and data collection is ongoing.	In some Member States patients/carers can report directly to the regulatory authorities.
PSUR		
1st paragraph	Clarification is requested about the meaning of "significant" off label use and the threshold for such significance.	Not incorporated. The MAH has to provide a breakdown by age in the section of the PSUR dealing with exposure.
2nd paragraph (or for post	One source of information on the use of medicines in children is from Prescription-Event Monitoring Studies. Such studies have included off label use (with regard to age) of medicines during the immediate post	Drug utilisation studies are mentioned in the text.

authorisation studies 4th paragraph)	marketing period. Such information would add to the information available from clinical trials on the paediatric use of medicines. Because of the small number of children in any one database, the real value of such data is when the information is pooled, whether using formal systematic analysis or informal review.	
2nd paragraph last sentence	Drug utilisation studies are not routinely performed by MAH. The collection of this information could be perceived as promoting off-label use	Drug utilisation studies are information gathering exercises. They do not promote use in one way or another.
2nd paragraph	The guideline requires detailed information on drug exposure (e.g. exposure broken down according to ICH ages, etc.). However providers of pharmaceutical market information do not routinely supply these data The wording of the requirement should reflect the practical difficulties MAHs may have to have access to this information.	Not incorporated as considered that drug exposure data are an important information to be provided. MAHs should make their best endeavours to supply such data.
3rd paragraph	Clarification is requested on the resetting of the PSUR cycle: is it triggered by the addition of a paediatric indication in EU or also by a first approval outside the EU?	Triggered by the addition of a paediatric indication in the EU.
3rd paragraph	The 2 sentences are proposed to be replaced by 'The addition of a paediatric indication for an existing medicinal product requires submission of 6-monthly PSURs for two years. Thereafter, the periodicity of the PSUR submission should be phased in with the PSUR submission schedule already in place.'	Incorporated.
	The use of independent data monitoring committees is valued.	Noted.
Published literature		
	It may be appropriate to provide a simple method for authors to supply pre-publication data to the EMEA and other authorities in such a way as to not prejudice publication.	Not incorporated. It is considered extremely difficult to establish a system for submitting these pre-publication data on a systematic basis. Should a third party wish to submit safety data pre-publication, then the regulatory authorities could review this on a case by case basis.
Post Authorisa-tion studies		

General	There are examples of medicines which become more widely used in children post-authorisation, so there is a strong need to study their use in children during the post-marketing period. We agree that specific post-marketing studies could be needed in certain circumstances.	Already incorporated.
1st paragraph	Don't I and II cover the same issue? Proposed addition of: "IV. If relevant, studies to investigate the mechanism of action of ADRs and to identify risk factors should be considered, so that appropriate risk minimisation activities in children can be considered".	I and II cover different issues. Not incorporated. This is part of III (those designed to evaluate known safety issues (e.g. those detected in the pre-authorisation phase))
2nd paragraph, 3rd line	Addition of "and in Good Epidemiology Practice Guidelines" after the reference to Volume 9.	Not incorporated. The word "rules" at the beginning of the sentence refers to the rules applicable in the EU regulatory framework. Good Epidemiology Practice Guidelines do not fall into this category.
3rd paragraph, last line	It should also be appropriate for a patient representative to participate and, where primary care patients are involved, a primary care physician.	Incorporated.
3rd paragraph	Data monitoring committee maybe appropriate for such studies.	Not incorporated. Not considered appropriate to include.
4th paragraph	The proposed arguments are very sound and motivated. However, perhaps because of the still limited use of databases and of their current not homogeneous quality properties, the outlook about their potentiality is insufficiently stressed. Database collecting, in a standardised quality controlled fashion, routine clinical data, even supplemented by storage of biological samples, represent the most important future resource for all the three categories of post authorisation safety studies, and they are able to answer research questions in the most rapid cost/effective and complete way, also including the potential for risk evaluation and benefit-risk assessment.	Not incorporated. There is no justification to stress the importance of databases over and above the other available tools.
4th paragraph	To maximise the use of such registries it may be appropriate to standardise minimum data collection for both patients receiving the medication under study and appropriate controls as minimum clinical practice for the use of such medications.	

	Databases used for such studies should record age of child accurate to one month and not one year.	Incorporated.
	Non-interventional studies, according to the definition provided, will not address the issue of off-label use. In addition, additional testing such as blood sampling, would not be possible.	Noted.
4th paragraph	Because of the small number of children in any database, the real value of such data is when the information is pooled, whether using formal systematic analysis or informally reviewed.	Incorporated.
7.2 Data Management		
	For ADR in the neonatal and early infant period, the gestational age of the child at birth should be documented.	Incorporated.
2nd sentence	Privacy Laws in some Member States may not allow recording of the date of birth in a database.	Noted.
7.3 Signal detection		
1st paragraph, 2nd sentence	"both the MAH and the regulatory authorities are responsible for making sure that processes are" should replace "processes should be".	Incorporated.
4th paragraph, last line	"Enhanced pharmacovigilance with data capture aids to get as complete information as possible, may be considered" should be added.	Incorporated with adjustment of wording and sited earlier in the section.
7.5 Regulatory action		
3rd paragraph	The capabilities of MAH to monitor off-label use appear limited and the options outlined may not all be feasible, especially when close cooperation with the prescribers is needed. Regulatory guidance is requested regarding the safety information for paediatric off-label use that should be included in the SPC in order that there are no negative consequences for the MAHs and that it is not considered as the promotion of an off-label use indication.	Noted. This relates to the EU Guideline on the summary of product characteristics that will be revised to reflect the paediatric regulation.
3rd paragraph	It is noted that there is limited information on the use of medicines in children in the community. One such source of information is from Prescription-Event Monitoring (PEM) studies, conducted by the DSRU, that monitors the use of newly marketed medicines prescribed	Drug utilisation studies are already mentioned in the text.

	by GPs in England. These studies have included "off label" use (with regard to age) of medicines, during the immediate post-marketing period. Information from PEM studies would add to the information available from clinical trials on the paediatric use of medicines.	
3rd paragraph	The MAH should not just monitor off-label use but also report it, the method for doing so should be agreed prospectively with regulatory bodies. It is striking that there is limited awareness of prescribing of unlicensed and high doses of inhaled and nasal steroids in children (in almost one in ten for inhaled steroids from recent evidence presented at the British Thoracic Society in December 2005). This may also be the case for new treatments such as new immunomodulating agents for the treatment of atopic dermatitis in very young infants. Such mechanisms should ensure this does not happen in the future.	This is part of the EU requirements for Periodic Safety Update Reports (Vol 9A of the rules governing medicinal products in the European Union).
3rd paragraph, 3rd and 4th sentences	A MAH can be expected to monitor off-label use to some extent, however the guideline also proposes that the MAH "actively collects safety data relating to such use" and proposes methods for collecting these data. It is feared that the other suggested methods outlined in the draft guideline may not all be feasible as they are somewhat intrusive on medical practice and may not always be compatible with privacy protection laws. These databases are not always readily available. The data contained can be complex to interpret, depending on for example the indication, the accuracy and completeness with which the information is recorded in the databases by prescribers. In these circumstances allowance for not supplying complete information should be made.	Comments noted. No change to the guideline proposed.
7.6 Communication		
1st paragraph, 3 last lines	Concerns were expressed about the inclusion of "child friendly information" in patient leaflet because the reading level and vocabulary varies among paediatric age groups and that a single text would not be adapted. The sentence "where appropriate, child friendly information should be included in the patient information leaflet, in a separate section if necessary" was proposed to be deleted since the inclusion of several wordings for differently age groups was considered unfeasible.	Not incorporated. The original text is preferred and has been retained. The current wording is clearly a suggestion for consideration and is not mandatory.

	It has also been suggested that this statement is revised to recommend inclusion of child-friendly information in the patient information leaflet pertinent to use in children where such advice is necessary for the safe and effective use of the product in that population.	Not incorporated. It is considered to include child-friendly information where appropriate without restriction.
1st paragraph, 3 last lines	Another concern was that it could set inappropriate ethical and regulatory precedents for manufacturers to communicate risk/benefit information directly to minors and that such interactions should be the responsibility of parents and guardians and clinicians who oversees patient care.	Not incorporated. This is considered to be an unhelpful approach in terms of the current information needs of the paediatric population.
1st paragraph	It is important that all data from MAHs is presented in a timely and transparent manner, and in an appropriate language for the intended target group.	Comment taken in account.
7.7 Audit and Outcome assessment		
	Clarification is requested about the scope and intent of this section. It is supposed the outcomes of action taken refers to actions similar to those proposed for Risk minimisation plans in the CHMP guideline on Risk Management Systems for Medicinal Products for Human Use. The level of details of this section is considered insufficient and the inclusion of specific criteria for requesting audit and outcomes assessment as well as the description of the associated regulatory processes (what will be measured, analysed…) is recommended.	Not incorporated. The section states clearly that audit of the pharmacovigilance process and assessment of outcome applies for paediatric Pharmacovigilance as for all other areas of Pharmacovigilance.
8. REFERENCES		
	The provision of specific EMEA contacts for discussing the implementation of the guideline was recommended.	Not incorporated. Specific EMEA contacts are not included in CHMP Guidelines.