European Medicines Agency

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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

PROPOSAL FOR A REVISION OF THE EUROPEAN COMMISSION GUIDELINE ON SUMMARY OF PRODUCT CHARACTERISTICS

OVERVIEW OF COMMENTS RECEIVED ON DRAFT REVISION 2 OF THE SmPC GUIDELINE

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This overview of comments first presents the general comments before addressing the specific comments on the guideline. The later have been integrated to the text of the guideline released for consultation and the changes resulting of the consultation are highlighted.

Organisations that commented on the draft Guideline as released for consultation

	Name of Organisation or individual	Country
1	Cambridge Regulatory Services	UK
2	European Association for the Study of Diabetes (EASD)	Germany
3	Medicines and Healthcare products Regulatory Agency (MHRA)	UK
4	Medical Products Agency (MPA)	Sweden
5	State Institute for Drug Control	Czech Republic
6	Alcon Laboratories	UK
7	International Plasma Fractionation Association (IPFA)	The Netherlands
8	Medicines Evaluation Board (MEB)	The Netherlands
9	Federal Institute for Drugs and Medical Devices (BfArM)	Germany
10	Italian Medicines Agency (AIFA)	Italy
11	F. Hoffmann-La Roche Ltd.	Switzerland
12	European Generic Medicines Association (EGA)	Belgium
13	Medical Dictionary for Regulatory Activities (MedDRA) - Maintenance and Support Services Organization (MSSO)	USA
14	Federal Highway Research Institute - European Integrated Project DRUID	Germany
15	GE Healthcare	UK
16	Medicine Evaluation Committee (MEDEV) of European Social Insurance Platform (ESIP)	Belgium
17	Pharmiceutics LLC	USA
18	European Biopharmaceutical Enterprises (EBE)	Belgium
19	European Vaccine Manufacturers (EVM)	Belgium
20	European Scientific Cooperative on Phytotherapy (ESCOP)	UK
21	Merck Sharp & Dohme (Europe) Inc.	Belgium
22	Spanish Association of Pharmacists in Industry (AEFI)	Spain
23	AstraZeneca	UK
24	European Specialists Nurses Organisations (ESNO)	Belgium
25	European Association for Clinical Pharmacology and Therapeutics (EACPT)	UK
26	Pharmaceutical Group of the European Union (PGEU)	Belgium
27	European Society of Cardiology (ESC)	France
29	Task-Force in Europe for Drug Development for the Young (TEDDY)	Italy
30	Association of the European Self-Medication Industry (AESGP)	Belgium
31	Standing Committee of European Doctors (CPME)	Belgium
32	Infarmed	Portugal
33	Irish Medicine Board (IMB)	Ireland
34	Pharmasymbiosis Ltd	UK
35	European Federation of Pharmaceutical Industries and Associations (EFPIA)	Belgium
36	Czech Republic QRD	Czech Republic

GENERAL COMMENTS

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AEFI	The review is welcomed as the SmPC is the basis for regulatory and commercial framework and the structure and content must be updated at the state of the art in science and technology.	The SmPC is primarily the basis of information for healthcare professionals on how to use the medicinal product safely and effectively.
Alcon Laboratories	Scientific literature should be included as one of the sources of information for the preparation of SPCs. This is not clearly specified in the text provided and it is especially relevant for post-marketing updates of the safety profile. Section 4.8 page 16. It is stated, "The whole section could be revised at the renewal of the MAA, where the safety profile of most products is likely well-established, and thereafter at each of the three yearly PSURs." It should be noted that currently this approach is not acceptable to many of the regulatory authorities. Does this revision to the SPC guidelines reflect a new approach by the regulatory authorities to the mechanism by which SPC's can be updated. How will this procedure work in practice and what fees will apply?	Sources of information for the preparations of the SmPCs are outside the scope of this guideline; refer to regulatory marketing authorisation requirements. This recommendation is consistent with the guideline on the processing of renewals in the centralised procedure which also reminds that none of the changes introduced at renewal should substitute for the marketing authorisation holder's obligation to update the marketing authorisation throughout the life of the product by variation procedure as data emerge.
AESGP	It is appreciated that the new version for the SPC-Guideline reflects the requirements of recently published guidelines to address storage advice and particularities in terms of herbal medicinal products. However, the guideline appears now more complicated than in the past as general recommendations and didactic statements are intertwined. A more consistent approach would be beneficial. In addition, some guidances are more complicated than previously e.g. frequency calculations. We question whether this is helpful. In general the guideline accommodates the requirements of the paediatric indication effectively. However there appears to be an excessive emphasis on paediatric data which has the knock-on effect of appearing to downplay other data e.g. renal toxicity, hepatotoxicity and elderly data. We do not believe that this is appropriate nor do we believe that including information on paediatric use in almost every section of the SPC is actually of benefit for the practitioners. The additional information on pharmacogenetic data and the newly proposed structure of Section 4.8 "Undesirable effects" (differentiation of adverse reactions from clinical trials, post-authorisation	The principles set-out in this guideline are applicable to all medicinal products. The application of those principles for a particular medicinal product will depend on the scientific knowledge on the medicinal product, the legal basis of a marketing authorisation and public health needs. The guideline makes recommendations on how to include paediatric information according to the new paediatric regulation. Guidance has been prepared with the aim that the information necessary for healthcare professionals is presented without over-information.

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	safety studies and spontaneous reporting) will not be applicable for well-established products which have been on the market for one to several decades. This makes sense for future-oriented development of any ongoing or planned clinical development but not for already marketed products. For the reasons stated above, the guidance should only be applied prospectively and not retrospectively. For older products the data are simply not available or are not appropriate for the more sophisticated analyses proposed. For clarity purposes, it would be helpful to include suggested SmPC statements in a frame so as to clearly distinguish explanations to suggested sentences/statements.	
AstraZeneca	AstraZeneca would like to point out specifically that if the proposed changes to the guideline are implemented with immediate effect this would cause great administrative burden and a significantly increased workload for Industry and Regulators and so it is assumed that a realistic timeframe for implementation is foreseen.	This guidance shall apply as from 1 May 2010. However, submissions may also be done on the basis of this guidance prior to that date. The principles set-out in this guideline are applicable to all medicinal products. The application of those principles for a particular medicinal product will depend on the scientific knowledge on the medicinal product, the legal basis of a marketing authorisation and public heath needs. The SmPC is the basis of information for healthcare professionals on how to use the medicinal product safely and effectively. Timing for updating the SmPC according to this revised guideline should therefore be driven by this objective. The revised guideline can be implemented for new marketing authorisations without delay. For existing authorisations, renewal and applications based on new information (e.g. submission of extension of indications) represent a good opportunity to update SmPC. This should not substitute for the marketing authorisation holder's obligation to update the marketing authorisation throughout the life of the

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		product by variation procedure as data emerge.
Cambridge Regulatory Services	When do you expect this guideline to become mandatory? Do all existing SmPCs should be reviewed and when by? Should be submit as Variations? How the changes to the SPC affect generics companies and parallel importers?	See above
CPME	CPME would like to thank you for the opportunity to comment on the revision of the guideline on SPCs, also as member of the EMEA Healthcare Professionals Working Group. CPME welcomes the proposed revision of the Summary Product Characteristics guideline. Precise information on the use and effects of medicinal products in special patient groups, and the specific aspects that should be considered in these cases, serve patient safety and the effectiveness of medicinal treatments. Any initiative to improve the clarity of the SPCs is highly welcome, being tabulated summaries a good example. This should favour the functioning of the daily medical practices, and at the same time, the empowerment of an informed patient. The patient-doctor relationship in information is fundamental. The starting point for all exchange of information is the peer to peer dialogue with the patient. In this framework of the patient-doctor conversation, information to support the dialogue is also provided such as medical advice on the product prescribed. CPME therefore supports the proposed revision of the SPCs guideline as it aims to provide further clarification, and ultimately, to improve patient safety.	
Coordinator BASt (Bundesanstalt fuer Strassenwesen) of the European DRUID project (Driving under the influence of drugs, alcohol and medicines)	The DRUID Partners involved in categorizing the impairing effects of medicinal drugs affecting driving performance have discussed the SPC paragraph 4.7 during their recent meeting in Paris (29th February 2008) and agreed upon adding more specific information to the description of conditions and circumstances that need to be considered for informing patients on the effects of the medicine on the ability to drive and use machines.	
EACPT	The European Commission guideline on Summary of Product Characteristics has been carefully revised. Many changes are straight forward and consider major modern issues of personalized medicine considering physiological, pathophysiological and genetic properties as well as special populations. These changes are considered as major progress and could contribute to a more rational and safer drug therapy.	
EASD	EASD considers the SmPC to be especially important in the field of diabetes. Several different types of	These comments are acknowledged. Some

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	drugs have been introduced recently for diabetes, lipids and blood pressure that will be used by non-specialists as well as specialists. There are also important up-dates for some established drugs in the field. EASD welcomes plans for greater consistency of format and terminology, and more concise phraseology. It may be helpful to introduce a succinct practical summary at the beginning of the SmPC that briefly identifies key prescribing information: eg. most common uses of the agent, how it is used, important contraindications, cautions and monitoring (eg the brevity of the BNF or similar concise formulary documents). It might be helpful to list available tablet strengths and identification description of the tablets at beginning in summary.	information on availability of different strengths and description identification is possible. Revising the structure of the SmPC or asking for more information on the different strengths available would necessitate a revision of the legal framework (e.g. the current legal framework asks for one SmPC per strength).
EBE	The current document does not advice on how to provide transparent data on similar biological medicinal products, and the SmPCs published to date for biosimilar products are relatively confusing, and structured inconsistently. Since there may be clinically significant differences between the biosimilar product and the reference product, the practice of using the SmPC sections of the reference product that has been accepted for small molecule generics is not appropriate (see also comment on the section 5.1 below). The EMEA's "Questions and answers on biosimilar medicines" (EMEA/74562/2006) states: "Since biosimilar and biological reference medicines are similar but not identical, the decision to treat a patient with a reference or a biosimilar medicine should be taken following the opinion of a qualified healthcare professional." In order for the healthcare professional to form such an opinion, it is essential that the necessary information is readily accessible in the relevant SmPCs. EBE therefore proposes that the points highlighted in the EBE-EFPIA *Position paper on labelling of biosimilar medicinal products* (28 March 2007) should be reflected in the guideline on the SmPC. In the guideline it should be advised that the contents of the SmPC for a biosimilar product cannot simply be copied from the reference product SmPC, and that the following information should be included in the biosimilar product SmPC: • Clarity that the biosimilar registration route has been used. • What is the reference product used in the studies.	Full transparency on the authorisation of biosimilar medicines is ensured with the publication of EPAR. A biosimilar can be authorised if the application shows that the biosimilar medicine is similar and as safe and effective as the biological reference medicine. The SmPC is the basis of information for healthcare professionals on how to use the medicinal product safely and effectively. Therefore in the case of biosimilar, it should be consistent with the SmPC of the reference product. To further ensure transparency, it is proposed to include at the beginning of section 5.1 of SmPC of biosimilar, a statement informing that the product is a biosimilar with a reference to the EMEA website for detailed information.

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	• What studies have actually been carried out with the biosimilar product and overview of data obtained. • What are the safety data available on the biosimilar product. • Statement on interchangeability/ automatic substitution. In order to avoid confusion, the specific product names should be allowed to be used in the SmPC instead of the INN, as the use of the same INN for several biological products does not mean that the active substances are identical. This allows for clear discrimination between statements relating to the biosimilar itself, and those relating to or derived from the reference product.	
EFPIA	Industry appreciates the opportunity to comment on the revision of the above-mentioned guideline. In general, the clarifications are clear and improve the quality of the document. This revised draft guideline provides useful guidance on the format and content of the SmPC that should improve consistency and clarity of labelling for the benefit of the healthcare community and patients. However, a number of concerns remain, which need to be addressed in order to ensure that the guidance remains sufficiently flexible and results in a SmPC that is manageable for all stakeholders (prescribers, industry and regulators) both in terms of format as well as content. The most important ones are listed in the section General comments. More detailed comments are provided below.	Comments acknowledged.
	Content-related: The primary focus of the SmPC appears to be to describe "risk", and there is little opportunity for the communication of the benefits. Proposed amendments to section 5 of the SmPC are of great concern, as they will further exacerbate this imbalance in the communication of benefit/risk, as well as introducing an imbalance between the type and quantity of information provided on adult efficacy and that on paediatric efficacy. Products with multiple authorised indications would also be penalised, as the information that could be included on each individual indication would be severely limited. MAH must be given ample opportunity to communicate information which is of relevance to the patient and the prescriber and alternate proposals are listed in the specific comments section.	It is supported that the SmPC should ensure the appropriate balance between the risks and the benefits of the medicine. The SmPC guideline should be carefully implemented to assure this balanced information.
	On the basis of various practical experiences over the past years, we still have concerns regarding the interpretation of especially Section 4.8 of this guidance. From these experiences it appears that the presentation of adverse events and the determination of the frequency is an extremely complex matter, which may lead to many discussions and differences	Determination of frequency of adverse reaction is a matter of scientific assessment. Standard principles have been presented in this guideline together with clarifications on the presentation of the information

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	in interpretation also on the side of the regulator. Some alternative proposals are given in the specific comments section. We note the Commission's proposals to amend Article 11 of Directive 2001/83/EC to include "Key Safety Information" in the SmPC (included in the Commission's December 2007 public consultation on legislative proposals under their "Strategy to Better Protect Public Health by Strengthening and Rationalising EU Pharmacovigilance").	in section 4.8, which should help to tackle concerns and heterogeneity experienced in the past for this section.
	The proposed revisions to the SmPC guideline need to be considered in concert with these legislative proposals, in order to ensure the best possible presentation of important information, and to avoid unnecessary multiple revisions to existing SmPCs. It appears that the "Key Safety Information" (SmPC section 3b in the legislative proposals) may be similar to the "Summary of the Safety Profile" (section 4.8, subsection (a) in the draft guideline), although the description of the latter is more useful and less ambiguous than the former. Furthermore, inclusion of this type of information in section 4.8 would be considered preferable as this is where the prescriber is more likely to look for safety information, rather than under section 3 Pharmaceutical Form, where it could be overlooked.	The term "serious" should be understood according to its regulatory definition. The term "important" is used to refer to medically important information. The term paediatric population is the appropriate term for general guidance. "Children" can be used in practice as far as the age range for which the information applies is specified.
	Inconsistent definition of terms: e.g. the term "serious" seems to be applied with different meanings in various places throughout the document. It is unclear whether the term refers to the regulatory definition of a serious ADR or whether it refers to a medically important condition. Another example is the incorrect use of the term 'children' when 'the paediatric population' is meant and the lack of a proper definition of age groups by e.g. an age range". We propose that the intended concepts be clarified throughout the guideline. In general the guideline accommodates the requirements of the paediatric indication effectively. However there appears to be an excessive emphasis on paediatric data which has the knock on effect of appearing to down play other data e.g. renal toxicity, hepato toxicity and elderly data. We do not believe that this is appropriate.	The comment on the need for separate SmPC for each form and strength is acknowledged but should be considered from a legal perspective. SmPC should be clear and concise. Both industry and regulator should apply the guideline towards this objective. The different sections of the SmPC may overlap. Repetition of information may overload the SmPC. An appropriate balance has to be found in practice between cross-referencing, amount of information and readability.
	Format-related: • The guideline still requests separate SmPCs for each pharmaceutical form and strength, because the European Commission and certain Member States require them. This requirement should be reconsidered, as the creation, maintenance and assessment of separate SmPCs for different forms and strengths of the same product waste authority and applicant resources and increase the	Other format-related comments may not be considered as a priority.

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	possibility of making errors. The fact that not all MS impose this requirement further indicates that it is unnecessary. • There is a definite risk that the SmPCs will become "oversized" in terms of overloading with formal elements, which would be in contradiction to the aim of presenting the essential information on a medicinal product in as clear a manner as possible. • Too much emphasis is placed on cross-referencing throughout this guidance. Cross-references should be reduced to a minimum, otherwise they may not be read. If cross-referencing is recommended with a specific wording, it should always respect the style introduced in the QRD templates by quoting 'see section X'. • The English content of the guideline needs to be improved (including consistency in use of terminology; e.g when rewording "liver disease" to hepatic impairment and "lactation" to "breast feeding; the use of correct MedDRA terminology such as Primary System Organ class instead of preferred System Organ Class and Lowest Level Term instead of Lowest Term Level). It would be helpful to include suggested SmPC statements in a list format (in a separate paragraph from the guidance itself) as it can get lost within the text – e.g. suggested sentences are given section 4.1 and 4.2, but could be easily overlooked). **Procedure-related:** Time line for implementation is needed. We believe that several aspects of the guideline can only be implemented prospectively and not retrospectively. For older products the data are simply not available or are not appropriate for the more sophisticated analyses proposed. The SmPC format changes in accordance with this new guideline for already approved products should therefore be done on voluntary basis at renewal or with an existing variation and without payment of additional fees. If PILs or labelling changes are required to maintain consistency, then the timing of the SmPC change and the PIL/labelling changes should only be linked where changes are regarded as critical for patient safety – since such changes if mandatorily linked could result in significant logistical manufacture & supply issues. Any implementation time frame should be at least 2years (starting from the date all QRD templates are available).	See answer to comment above.
EGA	The EGA welcomes the opportunity to comment on the draft proposal of the EC guideline on Summary of Product Characteristics. We accept all the changes proposed and are particularly pleased that the	Comments acknowledged.

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	abbreviation 'SmPC' is now used instead of 'SPC' which indeed stands for 'Supplementary Protection Certificate'. The EGA notes the amendments proposed for the section on biological medicinal products in part 2 of the SmPC. All the revisions to this section are considered acceptable. In particular, the EGA notes with satisfaction that no subsection on biosimilar medicines has been included since such products do not represent a category distinct from biological medicinal products/biopharmaceuticals and are covered in the revised section.	
ESCOP	ESCOP appreciates the revision of the Guideline on Summary of Product Characteristics because the text has been adapted to other specific guidance documents. ESCOP as a scientific organisation has used the structure of the SPC in the preparation of monographs on the medicinal use of plants for many years and is therefore interested in the specific content of the guideline.	
ESC	The European Society of Cardiology (ESC) represents more than 50,000 cardiology professionals across Europe and the Mediterranean. The ESC comprises 4 Councils for Cardiology Practice, 5 Associations, 19 Working Groups and 50 National Cardiac Societies Its mission is to reduce the burden of cardiovascular disease in Europe.	
ESNO	Excellent document, very useful for professionals information	
EVM	EVM believes that the new requirements in the revised guideline will apply to: • New products, as soon as the Guideline comes into force • Already authorised products taking the opportunity of a type II variation impacting the SmPC and when appropriate or technically feasible The revised SmPC guideline introduces new subsections for 'paediatric population'. EVM considers that the new "paediatric" subsections should not apply to products indicated only for paediatric use. Therefore, EVM suggests that the guidance could specify that these headings are mandatory only if the product includes an indication for population(s) beyond the paediatric population/group. EVM would also like to draw the attention to Article 87 of DIRECTIVE 2001/83/EC, which states that: "All parts of the advertising of a medicinal product must comply with the particulars listed in the summary of product characteristics." Therefore, it is critical that the relevant information provided in Section 5.1 of the SPC supports the information in promotional material. Therefore, EVM considers that	The principles set-out in this guideline are applicable to all medicinal products. See answer to comments in section 5.1

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	the limitation to one page wouldl not be possible in the case of vaccines.	
GE Healthcare Ltd	Would like to give positive feedback to the changes made to this guideline.	
AIFA	To use the wording "medicinal product" instead only "product". Often in the text is missed the term section in front of the number of the section (e.g. pages 9, 10, 12, 13, 17, 18, 23, 25, 26)	Not necessary
MedDRA MSSO	The MSSO welcomes the opportunity to comment on this proposal for a revision of the SmPC Guideline. We are pleased to see the recommendation for the use of MedDRA in the SmPC, and we support the pragmatic approach to modification of the MedDRA hierarchy in the context of the SmPC that is designed to make it more clinically meaningful to the reader. In Annex 2, where specific examples of MedDRA terms are cited, we recommend that the impact of MedDRA versioning be taken into account; instead of reviewing and updating the examples with each release, it may be more practical to insert a caveat in this section to indicate that the MedDRA term examples shown may not correspond to the current MedDRA version. We would be interested to know if there are any plans for the Guideline to require applicants to submit supporting documentation indicating the specific modifications made in the SmPC adverse reaction tables compared to the original source tables.	Comment acknowledged. The purpose of the SmPC guideline is to make recommendations on how to present information in the SmPC and not to create new data requirements. Information presented in the SmPC should be based on scientific data available at the time of the initial marketing authorisation or obtained post-authorisation.
MEDEV ESIP	The MEDEV Committee and ESIP welcome the initiative to update EC guideline on SmPC. Proposed changes will improve exactness of SmPC and safety for patients.	
MHRA Vigilance and Risk Management of Medicines Division	The revision to the guideline is welcomed, in particular in providing clearer information on the use of a product in paediatric population. As a general comment, there is existing guidance on the content of a vaccine SPC. There is a need to ensure that these are consistent (and applied consistently) and cross-referred.	Comment acknowledged.
Merck Sharp & Dohme (Europe) Inc.	MSD welcomes the proposed revisions to the SmPC guideline and specifically the updates and new principles proposed for section 4.8. We are concerned that product information is becoming more complex due to the inclusion of specific information related to risk management plans and paediatric indications broken down by age groups and that the readability of the document may be compromised as a result. We would recommend that specific focus interviews with healthcare professionals be held to ensure that the target	MSD's support for the new principles proposed on section 4.8 is acknowledged. The importance of interaction with healthcare professionals to ensure that they receive suitable information is acknowledged. In this respect, it should be noted that healthcare professionals' organisations have provided comments on this revision of

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	audience has a good understanding of the information provided. We also note that the SmPC has a tendency to state risks more prominently than benefits. This may give a false negative impression to prescribers and patients. We would prefer that the amount of information provided on risks and benefits is kept in balance to reflect the positive risk/benefit evaluation of a product during the regulatory approval process. The level of detail of information provided in the SmPC in relation to the level of detail provided in the EPAR should be considered. There maybe alternative ways to make available more detailed information in the EPAR and hence a shortening of the SmPC is possible if a weblink to the EPARs could be included. We would like to highlight, that a pragmatic approach for the phasing in of the revised SmPC requirements should be taken and that a retrospective application to SmPC text for approved products should be avoided.	the SmPC guideline. It is agreed that information provided must ensure a proper balance in terms of benefit and risk. The feeling that there is a tendency to state risks more prominently than benefits may be artificial because of the scope of the revision. The SmPC guideline should be carefully implemented to assure this balanced information. MSD's support for referring to the public assessment report for detailed information is welcomed See above regarding implementation of the revised guideline
PGEU	The revised SPC guideline is very good and provides further clarification, compared with the current guideline. It is also in line with comments made by the HCP WG, which is very welcomed. Among other positive and constructive additions, we particularly welcome the expanded section 4.8 as we believe this will provide important information to healthcare professionals when communicating benefits and risks of a medicine.	
Pharmiceut-ics' LLC	In several sections of the guideline it is unclear if a subheading is a subheading for the guideline text only, or if it is actually to appear in SmPC text. We suggest specifying which subheadings are intended to be used in an SmPC text, as it is done for section 4.8. And in some places, subheadings are placed in the guideline text so that they appear to cover information that clearly does not belong under the subheading (see for example the last two paragraphs in 4.4).	To be considered through the QRD templates. It is however acknowledged that use of subheading could facilitate reading in long section (e.g. 4.4) of the SmPC of some products.
Pharmasy-mbiosis Ltd	Information concerning this proposed revision was highlighted in the RAJ Journal issue of Feb 2008 with an actual link to the draft provided. I notice however that there is no mention of the proposed guideline revision in the 'What's new' section on the EMEA website or the 'latest news' section of the EUROPA website (unless of course I have missed it on both websites) and this might mean that there is the potential for insufficient scrutiny of the proposal as people may not be aware of its existence.	These concerns do not seem to be shared by other parties.

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	The revisions appear generally to employ the use of poor quality of language, grammar and in some instances the use of long and unwieldy sentences in the proposed update, none of which are helpful in maintaining the document as an authoritative guideline on the contents of an SPC. I hope you will agree that it is very important that this document is written in language that is both clear and precise so that it can be easily read and understood by its readership. Any ambiguity in its content provides the scope for misinterpretation or multiple interpretations, neither of which are desirable due to their potential impact on SPCs and as a result, on the wellbeing of patients.	
Roche	The SmPC is the basis for promotional claims and therefore companies should have the ability to make claims relating their products to competitors where there is good evidence base. The suggested changes in this document appear to be aimed at standardising statements about efficacy and excluding any claim relating to other products in a class. This is also the case for safety statements where so called class effects have to be included even if there is no evidence for these so called class effects in a particular product. The CHMP should make clear what the purpose of the SPC is. It should be a clear description of the product but should also be a guide to the practising prescriber, in which case excluding the possibility of making statements about a product might miss the opportunity of helping the prescriber.	The SmPC should not include promotional claims but should provide objective information to be the basis of information for healthcare professionals on how to use the medicinal product safely and effectively. This is particularly important in respect of Article 87of Directive 2001/83/EC, as amended, which states: "*1. Member States shall prohibit any advertising of a medicinal product in respect of which a marketing authorization has not been granted in accordance with Community law.* *2. All parts of the advertising of a medicinal product must comply with the particulars listed in the summary of product characteristics.* *3. The advertising of a medicinal product:* *- shall encourage the rational use of the medicinal product, by presenting it objectively and without exaggerating its properties,* *- shall not be misleading."*
TEDDY	TEDDY NoE strongly supported and still supports the process of paediatric drugs development, from the proposal to the implementation of the newly adopted Paediatric Regulation. TEDDY Experts contributed with suggestions and comments to several regulatory and scientific documents released for consultation by	

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	the European Commission and by the EMEA. The harmonisation and the update of the SPC in accordance with the new provisions established by the Paediatric Regulation represents an important step in the process aimed at increasing the number of drugs specifically addressed to children. A new updated SPC format including specific issues related to paediatrics is needed in order to better define the "drug identity card" to be used not only by Marketing Authorisation Holders and Regulatory Agencies, but also by practitioners, and parents and patients, the last drug users.	
-	-	Linguistic comments from various parties were also implemented.

MODULE 1.3 SUMMARY OF PRODUCT CHARACTERISTICS

Article 8(3)(j) of Directive 2001/83/EC and Article 6(1) of Regulation (EC) 726/2004 require that, in order to obtain a marketing authorisation, a Summary of Product Characteristics (SmPC) in accordance with Article 11 of Directive 2001/83/EC must be included in the application[1]. In accordance with Directive 2001/83/EC, when the marketing authorisation is issued, the Marketing Authorisation Holder shall be informed, by the competent authorities of the Member States concerned, of the SmPC as approved by it. For decisions concerning centralised marketing authorisations, according to Article 10 of Regulation (EC) No 726/2004, the final Commission decision with the SmPC is addressed and notified to the Marketing Authorisation Holder. Thus, the SmPC forms an intrinsic and integral part of the marketing authorisation.

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Pharmasy-mbiosis Ltd	Has there been a formal decision to adopt the abbreviation SmPC? It is my understanding that the abbreviation is meant to be SPC.	This proposed change in the abbreviation has followed the same consultation as any other revision proposed in this guideline. SPC is a regulatory abbreviation for Supplementary Protection Certificate. In order to avoid confusion the regulatory abbreviation for Summary of Product Characteristics is SmPC.

The SmPC sets out the agreed position of the medicinal product as distilled during the course of the assessment process. As such the content cannot be changed except with the approval of the originating competent authority.

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EVM	"As such the content cannot be changed except with the approval of the originating competent authority." Consider revising the above sentence as a number of changes of SmPC may not be eligible to an approval in the future variation legislation (for example: Change N°1. Change in the name and/or address of the marketing authorization holder - Type IA_{IN}) To add at the end of the sentence: "… *with the exception of administrative changes which may be submitted through a minor notification*".	For the purpose of this guideline, "approval" is to be interpreted broadly.

The SmPC is the basis of information for healthcare professionals on how to use the medicinal product safely and effectively. The Package Leaflet (PL) shall be drawn up in accordance with the SmPC. The *Guideline on excipients in the label and package leaflet of medicinal products for human use* is also applicable to the SmPC.

[1] Module 1.3 consists of the SmPC.

It is not in the remit of the SmPC to give general advice on the treatment of particular medical conditions. On the other hand specific aspects of the treatment related to use of the medicinal product or its effects should be mentioned. Similarly, general advice on administration procedures should not be included but any advice specific to the concerned medicinal product should be included.

This guideline provides advice on the principles of presenting information in the SmPC. Applicants should maintain the integrity of each section of the document by only including information in each section which is relevant to the section heading. However, some issues may need to be addressed in more than one section of the SmPC and in such situations the individual statements may cross-refer to other sections when these contain relevant additional information.

This guideline should be read in conjunction with any other specific guidance document related to the SmPC (e.g. on benzodiazepines, antibiotics, vaccines, pegylated proteins, or plasma-derived medicinal products).

Separate SmPCs are required for each pharmaceutical form and strength by the European Commission and certain Member States. Limited references to other strengths or pharmaceutical forms of the same medicinal product may be necessary in a SmPC if the dosage regimen is based on the use of several strengths or pharmaceutical forms. For the purposes of giving information to prescribers, the SmPCs of different pharmaceutical forms and strengths may be combined for appropriate products within the same range.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
Roche	Also include that cross-reference to other SmPC may be necessary if a different pediatric formulation exists. It is according to the draft now also required to include posology recommendations for the pediatric population in section 4.2 (see page 9). *Limited references to other strengths or pharmaceutical forms of the same medicinal product may be necessary in a SmPC if the dosage regimen is based on the use of several strengths or pharmaceutical forms, or if a different pediatric formulation exists.*	See related comment in section 4.2

SUMMARY OF PRODUCT CHARACTERISTICS: Principles of presenting information

- The SmPC should be worded in clear and concise language.

- Each section of the SmPC should first deal with those issues that apply to the core population for whom the medicine is indicated followed - when necessary – by specific information for any relevant special population (e.g. children or elderly).

- Public Assessment Reports provide detailed information on medicinal products and are available on the website of the European Medicines Agency, of Heads of medicines Agencies or other National Competent Authorities. A link to the relevant website ~~may~~ should be included in SmPCs when public assessment report is available.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
BfArM	In the second bullet point the Heads of Medicines Agencies should be stated as well, because the public assessment reports of applications granted by the decentralised or mutual recognition procedures will be published on their MRI-Product Index. Links should be added.	Agreed. See above
PGEU	We believe it would be beneficial and not a big effort to include the relevant link to the website with the (E)PAR. This will also help in disseminating the existence of the EPAR and the EMEA website and facilitate the HCP's work in accessing it! A link to the relevant website should be included in SmPCs. (instead of may)	Agreed. See above proposal
EFPIA	It is suggested that a link to the EMEA or National Competent Authorities websites in the SmPC (for the Public Assessment Report). Weblinks have limited utility for printed versions of the SmPC. In addition, web links can change and updates of the PARs on the EMEA webpage are considerably delayed. No revised wording proposed, as it is up to the companies to include such link.	Because of potential changes and updates, a link should direct to the relevant competent authority website and not to a more specific webpage. Because of stakeholders' expectation and need for transparent information, inclusion of such a link should be promoted

- ~~To avoid duplication of information, each section should first describe information applicable to the general population to be treated followed by specific information necessary for any subset(s) of the population (e.g. children or elderly).~~

- Consistent medical terminology should be used throughout the SmPC. ~~The use of MedDRA, at the "Preferred Term" level, is therefore recommended, in particular for sections 4.3, 4.4 and 4.8. When a Preferred Term is assigned to a preferred System Organ Class, the MedDRA hierarchy should be followed.~~ For example, the use of MedDRA as described in annex for section 4.8 should be applied though the SmPC, in particular for sections 4.3 and 4.4 and 4.8.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
Roche	MedDRA terms are often too broad. The terms chosen have to be consistent to what is presented on Annex 2. If term is too broad, specify the appropriated sub-term which better describes the event to avoid confusion	Comment acknowledged. Recommendations now refer to those in annex to the guideline.
MEDDRA MSSO	The third sentence in this paragraph is rather confusing in that it states that a PT has to be assigned to its preferred (primary?) SOC, according to the MedDRA hierarchy. This seems to contradict Annex 2 which allows flexibility in both primary SOC assignment and the application of grouping terms in the MedDRA hierarchy. If a term such as PT Liver function test abnormal is re-assigned to a "preferred" SOC Hepatobiliary disorders in the context of the SmPC, then the MedDRA hierarchy is not being followed. We suggest replacing the third sentence with one that states that certain modifications to the MedDRA hierarchy are permitted. Existing text: When a Preferred Term is assigned to a preferred System Organ Class, the MedDRA hierarchy should be followed. *In order to make the interpretation of adverse reactions simpler and clinically appropriate to the reader (and solely in the context of the SmPC), certain modifications to the MedDRA terminology are permitted (Annex 2).*	See above
Pharmiceut-ics LLC	This contradicts what is stated in section 4.8: "As a general rule, any adverse reactions should be assigned to the most relevant SOC related to the target organ. For example, 'Liver function test abnormal' should be assigned to the SOC 'Hepatobiliary disorders' rather than to the SOC 'Investigations' "	See above

The SmPC provides information on a particular medicinal product; therefore it should not include reference to other medicinal products (e.g. through statement such as "Like other medicines of the same class …") except when it is a~~n official~~ class warning recommended by a competent authority~~following a class review~~.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
Roche	not all known class warnings have an official recommendation issued by EMEA/Local HA; in these cases it would be useful, from a safety point of view, to use statement such as "like other medicines of the same class …"	Class warnings have to be validated by a competent authority Outside the scope of this recommendation.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	It seems unfair not to allow a comment that a certain adverse event is included because it has been seen in other drugs of that class when there is no evidence of it with the specific drug. … except when it is an official class warning recommended… must be followed for a cross reference to go to section "Warnings and precautions" It is mentioned that the SmPC is providing information on a particular medicinal product and that no reference to other medicinal products should be included. However, sometimes it is necessary to cross-refer to another product's SmPC eg. in section 4.2 when reference needs to be made to particular recommendations for a combination product; or in section 4.8 with ADRs that are particularly related to the combination partner in case the product is given in combination.	As stated in section 4.8 c; adverse reactions not observed with the product but which are considered to be related to the class, should be mentioned by stating the class attribution Guidance on cross-referencing is presented in individual sections. Outside the scope of this recommendation.
EBE	The guideline states that the SmPC provides information on a particular product, and should not normally include reference to other products. In the case of biosimilars, however, some information may be derived from the SmPC of the reference product, and some should be derived from studies with the biosimilar product itself, and there is a need to clearly distinguish between the sources of information. This should be made clear in this section. Amend as follows: "- The SmPC provides information on a particular medicinal product; therefore it should not include reference to other medicinal product (e.g. through statement such as "Like other medicines of the same class …") except when it is an official class warning recommended following a class review. In *the case of biosimilar medicinal products, however, some information may be derived from the SmPC of the reference product, and some should be derived from studies with the biosimilar product itself, and there is a need to distinguish between the sources of information as appropriate."*	See answer to EBE general comment.
EFPIA	Paragraph starting: "The SmPC provides information on a particular medicinal product: therefore it should not include reference to other medicinal products….". If medication is unlike others in the same class, or when it is usually used in combination with other products, this would mean that the SmPC does not provide this information. This would deny prescribers and patients' valuable information on which to base a treatment decision. In addition, this is not feasible in section 4.5 (interactions) where according to the same guidance, a "probe" can be used and its effects extrapolated to other substances of the same class.	This principle does not address potential differences between products of the same class. Such differences could be mentioned in the SmPC if useful to healthcare professionals and well established, e.g. as result of a clinical trial in section 5.1. Section 4.8 (and not 4.5) foresees to inform on adverse reactions with very

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	Either remove this statement or clarify that it is the trade name of the other products that should not be stated but that the active ingredients can be given if particular characteristics of a group of medicines are generally accepted.	low frequency or with delayed onset of symptoms which may not have been observed in relation to the product, but which are considered to be related to the same therapeutic, chemical or pharmacological class. The fact that this is a class attribution should be mentioned.
EVM	Although the reason of this sentence is to avoid excessive inappropriate labelling, this approach should be moderated. Information on the safety profile for new products introduced on the market is limited. The goal of adding adverse events of 'class effect' type is to improve the information intended to the Health Care Professionals. Adverse events based on common mechanism of action, most common adverse effects validated by scientific knowledge could constitute a useful base of potential adverse events. Moreover, class effects are not validated for all classes of products. For combined vaccines, the addition of references to the safety profiles of specific antigens already on the market may prove useful. *EVM suggests either to remove the sentence or to accept limited references to information available for particular valances/antigens, such as pertussis with well-known adverse reactions in the case of combination vaccines.*	Section 4.8 specifically foresees the possibility to inform of potential class effect to improve information on the safety profile of new products for which data are still limited. Case by case assessment will ensure appropriate and non-excessive application of this principle.
Pharmiceut-ics LLC	There are situations where it is appropriate to refer to another product or to a class of products. Sometimes it is important to refer to a risk as established for the class but not yet observed with the products; this can constitute a very proper warning about a class effect. Sometimes it may be necessary to mention other products recommended for prevention of undesirable effect, for the treatment of overdose. Sometimes a product may even only be approved as an adjunct to another form of treatment. The concern behind the proposed statement appears to be more about "improper" use of references to other products or a class than about the use references as such. We suggest that this be clarified.	See above.

- The principles set-out in this guideline are applicable to all medicinal products. The application of those principles for a particular medicinal product will depend on the scientific knowledge on the medicinal product, the legal basis of a marketing authorisation and public health needs. Deviation from this guideline should therefore be justified in the relevant Overview or Summary in the marketing authorisation application.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
Roche	It is specified now that deviations from this guideline need to be justified in the Overview or Summary. Just as a remark: this then needs to be done in a separate section to be added later in view of global filings and Overviews and Summaries that are normally to be used for submissions worldwide. This adds a bit to the complication for global filings if you need to be so specific wrt this EU guidance. Proposal would be to provide a Explanatory Note on top of the proposed SmPC in Module 1.3. that would outline the deviations from the EU SmPC guideline, thus keeping it separate from the global Overview and Summary documents.	ICH M4 E already asks that the clinical overview addresses how prescribing information and other approaches will optimise benefits and manage risks.
EFPIA	"public health needs": This term can be widely interpreted. E.g. it can be relevant for public health to include general information for education purposes. An example of this is the inclusion of a statement in the SmPC that Oral Contraceptives do not protect from HIV/Aids. It is important to specify the term 'public health need' especially because in the introduction the inclusion of such general advice is discouraged.	Public health is the ultimate objective. The sentence makes clear that public health needs are to be assessed depending on the product concerned.

- Practical advice on how to draw up the SmPC ~~ar~~ is provided to the applicant~~s~~ in the form of templates developed by the Quality Review of Documents (QRD) group, for centralised, decentralised and mutual recognition procedures.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
BfArM	The last bullet point is considering the templates developed by the QRD group but will in this form not mention the templates from CMD(h). Therefore a more general wording should reflect the general applicability of the templates. Links should be added. One typo needs to be corrected. *"Practical advice on how to draw up the SmPC are provided to applicants in the form templates developed by the Quality Review of Documents (QRD) group in cooperation with the Coordination Group on Decentralised and Mutual Recognition Procedures for Human Medicines [CMD(h)] for centralised, decentralised and mutual recognition procedures."*	Agreed with simplification; see above.
MSD	We recommend that the order of the bullets be revised in a logical way. Change order to read bullet 5, 6, 3, 4, 7, 1, 2	See above slight revision of the order.

1 NAME OF THE MEDICINAL PRODUCT

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
MEDEV / ESIP	In addition to the proprietary name an abbreviated name should be defined with maximum 60 characters with name, strength (of all active substances) and package. Many official names are too long for databases and have to be shortened and unified for everyday practical use (prescribing programmes, bulletins etc.).	See below
MHRA	Guidance states that the full standard term should be used in the product name offering no flexibility to use the short form where space is at a premium (even though section 3 implies the short form may be used on the label.) This will result in the use of two names, one on the SmPC and PIL and a different one on the label with possible confusion for patients or prescribers. Guidance needs to be amended so that a single product name is used. The guidance needs to clarify whether the name of the product is just the invented part of name (followed by form and strength) or whether the product name includes the invented part + form + strength. If the former then the sentence " *name followed by the strength and form*" does not make sense. If the latter then the sentence " *can be shortened to only the invented part of the name*" does not make sense. Clarify what is included in the name and correct other sentences as required.	Considering that: Article 11 states that "The SmPC shall contain (…) the name of the medicinal product followed by the strength and the pharmaceutical form", the current principle has been kept and the wording simplified for this section. Labels considerations are outside the scope of this guideline.
MHRA, Vigilance and Risk Management of Medicines Division	The name in section 1 should be revised to state that a shortened and patient-friendly pharmaceutical form is used as part of the name to enable clear and safe labelling to be used for both sighted and blind/partially sighted medicines users - including health care professions who often have to attempt to read small text in emergency situations. The rational for this is that the current requirement to include the full standard term in respect of the pharmaceutical form has major implications for the labelling of all medicines. The labelling provisions require that the name (including the strength and form) appear on the label. Often the full standard term is cumbersome and meaningless to patients and sometimes to healthcare professionals. It is difficult to display some names legibly on outer cartons and this is particularly problematic on small immediate packaging such as ampoules and vials. Over-the-counter (OTC) names again are a problem with the umbrella branding making for very long names. The Braille provisions require that the name in section 1 is displayed in Braille including form and strength where more than one of each of these exists. Long pharmaceutical forms mean problems for Braille	See above

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	placement	
ESNO	Names in different countries (i.e. hypnovel and versed)	There is a single name requirement for the centralised procedure.

~~*(Invented) name of the medicinal product, strength, pharmaceutical form*~~

~~In those sections of the SmPC in which full information on the name of the medicinal product is specifically required, t~~The (invented) name should be followed by both the strength and the pharmaceutical form. However, when otherwise referring to the medicinal product throughout the SmPC text, the strength and the pharmaceutical form do not have to be mentioned in the name. The International Non-proprietary Name (INN) or the usual common name of the active substance should be used when referring to properties of the active substance(s) rather than those of the product.

The use of pronouns (e.g. "it") is encouraged whenever possible.

Strength

The strength should be the relevant quantity for identification and use of the product and should be consistent with the quantity stated in the quantitative composition and in the posology. Different strengths of the same medicinal product should be stated in the same way, e.g. 250 mg, 500 mg, 750 mg. The use of decimal points should be avoided where these can be easily removed (e.g. 250 microgram, not 0.25 mg). However, where a range of medicinal products of the same pharmaceutical form includes strengths of more than one unit (e.g. 250 microgram, 1 mg and 6 mg), it may be more appropriate in certain cases to state the strengths in the same unit for the purpose of comparability (e.g. 0.25 mg, 1 mg and 6 mg). For safety reasons, micrograms and millions (e.g. for units) should always be spelled out in full rather than be abbreviated.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
MEDEV / ESIP	There are different aspects how to define the strength: From the viewpoint of informatics it should be stated that the denomination of strength must be in harmony with the package size. For example if the package size is 500 ml in case of a suspension then the strength must be given for 1 ml and not for 5 ml or in case of insulins if the package consists of 2 vials each containing 5 ml then the strength must be given for one vial (300 IU) and not for 1 ml. This could help the calculation of the total amount of active substances in the package which is of great importance for calculating reimbursement. From the viewpoint of physicians, pharmacists and patients for some medicines the other declaration is needed. For example suspensions especially for the treatment of children have got a spoon or a small beaker within and information about the content of the spoon or cup is important for the correct dosage. Preferably, where necessary, both types of strength should be declared.	There is currently a reflection on the expressions of strength at the level of the QRD group.

	For medicines with more active ingredients the strength should be defined in the same way as defined in ATC classification (for example Caduet 5/10 contains according to producer 5 mg of amlodipin and 10 mg of atorvastatin but in ATC classification it is defined as atorvastatin/amlodipin and in the group of statins, other combinations (C10BX). Similar example is Avandamet. For pancreatic enzymes and similar medicines is important that the strength is defined in comparable units (all in mg, IU or preferable in both).	

Pharmaceutical form

The pharmaceutical form of a medicinal product should be described by a single full Standard Term of the European Pharmacopoeia using plural form if appropriate (e.g. tablets) (see section 3). If an appropriate standard term does not exist, a new term may be constructed from a combination of standard terms in accordance with the document "Standard Terms, Introduction and Guidance to use". Should this not be possible, the competent authority should be asked to request a new Standard Term from the European Department for the Quality of Medicines (EDQM) of the Council of Europe. No reference should be made to the route of administration or container unless these elements are part of the standard term or where there is a particular safety reason for ~~its~~ their inclusion or where there are identical products, which may be distinguished only by reference to the route of administration or to the container.

For the expression of the name and strength of (traditional) herbal medicinal products the declaration should be in accordance with existing quality guidelines on herbal medicinal products.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
ESCOP	We appreciate inclusion of further quality guidelines as a reference for the expression of the name and strength of the product, because reference e.g. to the "Guideline on Declaration of Herbal Substances and Herbal Preparations in Herbal Medicinal Products / Traditional Herbal Medicinal Products in the SPC" may lead to transparency and uniform declaration of the products. Section 2: For the same reason, we welcome inclusion of further quality guidelines as a reference for the qualitative and quantitative declaration of the product and the active substance.	Comments acknowledged
MEDEV / ESIP:	*"The pharmaceutical form of a medicinal product should be described by a single full Standard Term of the European Pharmacopoeia using plural form if appropriate (e.g. tablets)*". PROPOSAL: …and official abbreviation (tab or tbl for tablets etc.). This would simplify and unify databases used for the informational support for electronic prescribing, analyses etc.	The request for facilitating the use of the SmPC in electronic tools is acknowledged. This however needs to be considered in a specific project looking at the whole SmPC to facilitate its use in electronic tools.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Full details of the qualitative and quantitative composition in terms of the active substance(s) and excipients, knowledge of which are essential for proper administration of the medicinal product, should be provided in section 2 and as appropriate in section 4.3 or 4.4. For example, excipients listed in the Annex to the "*Guideline on the excipients in the label and package leaflet of medicinal product for human use*" should be stated here under a separate subheading qualitatively, and, quantitatively ~~when its potential effect is dose-dependent (i.e. in practice, the quantity should be stated when the threshold given in the annex to the above guideline differs from zero).~~ ~~A~~ The following standard statement should be included at the end of the section, i.e. '~~<~~for full list of excipients, see section 6.1~~>~~'.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
EFPIA	According to current QRD templates, a statement on excipients in this section is introduced by 'Excipients:' – a separate subheading should not be required. The new proposed wording should be in line with the Annex to "Guideline on the excipients in the label and packaging leaflet of medicinal products for human use." (or could refer to it) A number of excipients e.g. sucrose & other sugars (glucose, galactose, fructose) have two thresholds, i.e. *'zero'* and '*greater than Xg/dose'. (see as an example Sucrose in the excipient guidelines)* In this example, only if the amount of the excipient in the product is above the highest threshold stated should the amount be listed quantitatively. For example, excipients listed in the Annex to the "*Guideline on the excipients in the label and package leaflet of medicinal product for human use*" should be stated here ~~under a separate subheading~~ in a separate paragraph introduced by 'Excipients:' qualitatively, and, quantitatively when its potential effect is dose-dependent (i.e. in practice, the quantity should be stated when the (highest) threshold given in the annex to the above guideline differs from zero and this threshold is exceeded with the recommended daily dose). A standard statement should be included at the end of the section, i.e. 'for full list of excipients, see section 6.1'.	"Excipients;" will be an appropriate subheading. The wording refers to the annex of the guideline on excipients. It cannot be excluded that a patient takes two different medicines with the same excipient whereby the total amount between the two products may lead to an effect. Quantity should therefore be stated as soon as the effect is dose-dependent, independently of the total amount for one product. See also below.
AESGP	A number of excipients e.g. sucrose & other sugars (glucose, galactose, fructose) have two thresholds, i.e. *'zero'* and '*greater than Xg/dose'. (see as an example Sucrose in the excipient guidelines: http://www.emea.europa.eu/pdfs/human/productinfo/ 3bc7a_200307en.pdf which has the following thresholds:* • *Zero: If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product* • *5g: Contains x g of sucrose per dose. This should be taken into account in patients with*	The proposal is consistent with the current wording. However it is acknowledged that the fact that two or more thresholds are presented for some excipients in the guideline on excipients may be confusing sometimes. It may also be confusing for the public to have the quantity of sucrose in one SmPC and not in another. Quantity should therefore be

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	diabetes mellitus. We do not think that the quantitative amount should be provided for all excipients with thresholds above zero. Only if the amount of the excipient in the product is above the highest threshold stated should the amount be listed quantitatively. Thus in the example above, the amount of sucrose would only need to be listed quantitatively if it contained 5g or more in the medicinal product. We propose that where the amount of excipient in the product is less than the highest threshold then it should not be listed quantitatively.	systematically presented when the effect is dose-dependent independently of the threshold or the route of administration. See below.
IMB Pharmacy Group	Where an excipient exceeds the threshold in the Excipient guideline it therefore has action or effect, and knowledge of it would be essential for the proper administration of the product. It should therefore be included quantitatively as required by the Directive. The inclusion of an excipient quantitatively provides the healthcare professional with information on the quantities involved and allows them to compare products and decide on the relevance and risk/ benefit of a particular product for the patient in their care. Although an excipient which has a zero threshold is known to have an action or effect, unless the product contains an excipient which precipitates an allergic reaction, there may be cases where the benefit of a medicinal product would outweigh the risk depending on the amount contained in the product e.g. in topical use benzoic acid as an excipient is 'mildly irritant to the skin, eyes and mucous membrance' and therefore inclusion of the quantity present would be beneficial *Proposed revised text:* *"For example, excipients listed in the Annex to the "Guideline on the excipients in the label and package leaflet of medicinal product* *for human use" should be stated here under a separate subheading qualitatively and quantitatively when they are present above the lowest relevant threshold in that guideline (even if the threshold is zero).* ~~*when its potential effect is dose-dependent (i.e. in practice, the quantity should be stated when the threshold given in the annex to the above guideline differs from zero).*~~ *"*	It is acknowledged that an effect may be dose-dependent despite having a zero threshold. Based on all above mentioned comments, it is confirmed that quantity should be stated for excipients with dose-dependent effect, independently of the threshold. Information provided in the guideline is not systematically presented in this way. Stating quantity may be helpful for safe use and such information which will not overload the SmPC. Considering the above and that transparency must be ensured for all aspects related to safe use of medicine, it is proposed to state the quantity of all excipients with known effects, such as those listed in the annex to the guideline
Pharmasy-mbiosis Ltd	Proposed rewording: *"..should be stated when the zero threshold is exceed, as per the guideline annex*"	See above
IPFA	Should we add "Paediatric" when the presentation is specific to this population?	To be addressed in relation to the name

If a diluent is part of the medicinal product, information should be included in the relevant sections (usually sections 3, 6.1, 6.5 and 6.6).

Qualitative declaration

The active substance should be declared by its recommended INN, accompanied by its salt or hydrate form if relevant, or the European Pharmacopoeial name if that name represents an established name in Europe. If no INN exists, the European Pharmacopoeia name should be used or if the substance is not in the pharmacopoeia, the usual common name should be used. In the absence of a common name, the exact scientific designation should be given. Substances not having an exact scientific designation should be described by a statement on how and from what they were prepared. References to the pharmacopoeial quality should not be included.

Where the medicinal product is a (traditional) herbal medicinal product, the qualitative declaration should be in accordance with the existing quality guidelines on herbal medicinal products.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
AESGP	We appreciate the update with regard to herbal guidance documents. The reference to the "guideline on declaration of herbal substances and herbal preparations in herbal medicinal products / traditional herbal medicinal products in the SPC" will contribute to ensure consistency in the declaration of the medicines.	Comments acknowledged

When the medicinal product is a radiopharmaceutical kit, the qualitative declaration should clearly indicate that the radioisotope is not part of the kit.

Quantitative declaration

The quantity of the active substance ~~must~~should be expressed per dosage unit (for metered dose inhalation products, per delivered dose and/or per metered dose), per unit volume, or per unit of weight and ~~must~~should be related to the declaration of strength in section 1.

Quantity should be expressed in internationally recognised standard term which could be complemented with another term if more meaningful to healthcare professionals. ~~Quantity should be expressed in terms which are meaningful to the prescriber. For example, sodium or potassium concentrations of an oral rehydration solution should be given in mmol/l.~~

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
EFPIA	It may be difficult to express quantity in a term which is meaningful for prescribers whatever the EU MS. Practices differ among MS (e.g. 0.9% w/v sodium chloride solution - 9 mg/ml sodium chloride solution - sodium chloride 9 mg/ml (0.9%) solution). Would it be acceptable to reflect theses differences in SmPC translations? We propose to delete the section: ~~Quantity should be expressed in terms which are meaningful to the prescriber. For example, sodium or potassium concentrations of an oral rehydration solution should be given in mmol/l.~~	The wording has been revised to accommodate potential different expectations from healthcare professionals.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
EVM	"Quantity should be expressed in terms which are meaningful to the prescriber. For example, sodium or potassium concentrations of an oral rehydration solution should be given in mmol/l." EVM considers that the unit (mmol/l) used in this particular example should be mg/l. To add more concrete examples would be useful. Propose to modify as follows: *"...For example, sodium or potassium concentrations of an oral rehydration solution should be given in mg~~mol~~/l".*	See above

Salts and hydrates

Where the active substance is present in the form of a salt or hydrate, the quantitative composition should be expressed in terms of the mass (or biological activity in International (or other) units where appropriate) of the active ~~entity~~ moiety (base, acid or anhydrous material), e.g. '60 mg toremifene (as citrate)' or toremifene citrate equivalent to 60 mg toremifene'.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
Pharmasy-biosis Ltd	replace 'entity with 'moiety' for the sake of consistency throughout the document?	Agreed

Where a salt is formed *in situ* during the ~~handling~~ preparation of the finished product (i.e. formed during the mixture of a solvent and powder), the quantity of the active ~~entity~~ moiety should be stated, with a reference to the *in situ* formation of the salt.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
Roche	Term "handling" seems not accurate in this case. "Preparation" (or reconstitution or mixture as alternatives) might well be used instead. Where a salt is formed *in situ* during the preparation of the finished product …	Agreed

In the case of established active substances in medicinal products where the strength has traditionally been expressed in the form of a salt or hydrate, the quantitative composition may be declared in terms of the salt or hydrate, e.g. '60 mg diltiazem hydrochloride'. This may also apply when the salt is formed *in situ.*

Esters and pro-drugs

If the active substance is an ester or pro-drug, the quantitative composition should be stated in terms of the quantity of the ester or pro-drug. When the active moiety is an active substance of an already approved medicinal product, the quantitative composition should also be stated in terms of the quantity of this active moiety (e.g. 75 mg of fosphenytoin is equivalent to 50 mg of phenytoin).

Oral powders for solution or suspension

The quantity of active substance should be stated per unit dose if the product is a single-dose preparation or otherwise per unit dose volume after reconstitution; a reference to the molar concentration may also be appropriate in some cases.

Parenterals excluding powders for reconstitution

For single-dose parenterals, where the total contents of the container are given in a single dose ('total use'), the quantity of active substance(s) should be stated per presentation (e.g. 20 mg etc.) not including any overages or overfill. The quantity per ml and the total labelled volume should also be given.

For single-dose parenterals, where the amount to be given is calculated on the basis of the patient's weight or body surface or other variable ('partial use'), the quantity of active substance(s) should be stated per ml. The quantity per total labelled volume should also be given. Overages or overfills should not be included.

For multi-dose and large volume parenterals, the quantity of active substance(s) should be stated per ml, per 100 ml, per 1000 ml, etc. as appropriate, except for multidose vaccines containing 'n' doses of the same dose. In this case, the strength should be expressed per dose volume. Overages or overfills should not be included.

Where appropriate, e.g. for X-ray contrast media, and parenterals containing inorganic salts, the quantity of active substance(s) should also be indicated in millimoles. For X-ray contrast media with iodine-containing actives substances, the quantity of iodine per ml should be stated in addition to the quantity of the active substance.

Powders for reconstitution prior to parenteral administration

When the product is a powder to be reconstituted prior to administration, the total quantity of active substance in the container should be stated not including overages or overfills, as well as the quantity per ml when reconstituted, unless there are several means of reconstituting, or different quantities used, which result in different final concentrations.

Concentrates

The quantity should be stated as the content per ml in the concentrate and as the total content of the active substance. The content per ml when diluted as recommended should also be included unless the concentrate is to be diluted to within a range of different final concentrations.

Transdermal patches

The following quantitative details should be given: the content of active substance(s) per patch, the mean dose delivered per unit time, and the area of the releasing surface, e.g. 'Each patch contains 750 micrograms of estradiol in a patch size of 10 cm^2, releasing a nominal 25 micrograms of estradiol per 24 hours'.

Multidose solid or semi-solid products

Quantity of active substance should be stated, where possible, per unit dose, otherwise per gram, per 100 g or percentage, as appropriate.

Biological medicinal products

Expression of strength.

The quantity of biological medicinal products should be expressed in terms of mass units, units of biological activity, or International Units as appropriate for the particular product, and reflecting *European Pharmacopoeia* usage where relevant. For pegylated proteins, the CHMP *Guideline on the Description of Composition of Pegylated (Conjugated) Proteins in the SmPC* should be referred to.

The biological origin of the active substance.

The origin of the active substance should be defined briefly. Thus, the nature of any cellular system(s) used for production and, if relevant, the use of recombinant DNA technology should be specified. The

entry should take the form: "produced in XXX cells <by recombinant DNA technology>". The following are examples of the application of this principle~~what should appear~~:

"produced in human diploid (MRC-5) cells",

"produced in *Escherichia coli* cells by recombinant DNA technology",

"produced in chick-embryo cells",

"produced~~purified~~ from the plasma of human donors",

"produced~~purified~~ from human urine",

"produced~~purified~~ from ~~animal~~ <animal>blood",

"produced~~purified~~ from porcine pancreatic tissue",

"produced~~purified~~ from porcine intestinal mucosa".

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
ROCHE	1/ …produced in *Escherichia coli* cells…, the word cells must be deleted. *E. coli* is a bacteria 2/ … purified from animal blood…, say which animal is	1/ Current wording correct. ***2/ proposed revision:*** "produced from <*animal*> blood"
EACPT	"purified from animal blood", Provide name of specific species e.g. purified from sheep blood	Agreed; see above proposed change.
MSD	"Porcine pancreatic tissue" and "porcine intestinal mucosa" Sensitivity issue, especially religious driven issue. Recommendation: Avoid this level of detail in the SPC, unless the quality and safety and efficacy of the final product is affected.	Transparency should prevail

Special provisions for normal immunoglobulins.

In the case of normal immunoglobulins, the IgG subclass distribution should be stated in terms of percent of total IgG present. The upper limit of the IgA content should follow.

Special provisions for vaccines.

In the case of vaccines, the content of active substance per dose unit (e.g. per 0.5 ml) should be stated. Adjuvants, if present, should be stated qualitatively and quantitatively.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
PDCO	Impurities that are of special relevance for paediatric populations (e.g ovalbumin in egg derived vaccines) should be specified by stating the maximum amount in the product.	Comment taken into account: see addition below

Residues that are of special relevance (e.g. ovalbumin in egg derived vaccines) should be specified.

Additional specific guidance is available in CHMP guidelines on biotechnological medicinal products, e.g. the CHMP Guideline on the Pharmaceutical Aspects of the Product Information for Human Vaccines.

Herbal medicinal products

The quantitative declaration should be in accordance with the existing quality guidelines on herbal medicinal products.

2 PHARMACEUTICAL FORM

The pharmaceutical form should be described by a full standard term of the European Pharmacopoeia (see section 1) using the singular form. The term used in this section should be the same as the term used in section 1. However, where a short standard term of the European Pharmacopoeia is used on small immediate packaging material, the short term should be added in brackets in this section.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
EFPIA	Addition of "using the singular form" contradicts the advice in Section 1 Pharmaceutical Form to use "plural form if appropriate (e.g. tablets)." The possibility or need to use a combination of terms, e.g. "emulsion for infusion or injection" should be mentioned. Recommend use of same wording in Section 3 as used in Section 1 for consistency i.e. "using plural form if appropriate (e.g. tablets)."	The plural is proposed as appropriate in section 1 to reflect the content of the presentation. The single form is use here to describe the pharmaceutical form. Please refer to the European Pharmacopoeia regarding use of combination of terms.

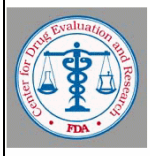
A visual description of the appearance of the product (colour, markings, etc.) ~~must~~ should be given, in a separate paragraph to the standard term, including information on the actual size of a solid oral formulation~~, or, on pH and osmolarity, as appropriate~~, e.g.

'*Tablet*

White, circular flat bevelled-edge tablets of 5 mm marked '100' on one side'

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
AESGP	The tablet size is detailed technical information which does not seem relevant for the SmPC. In addition, it may not always be possible to provide such information in a simple way (e.g. case of an oval tablet or more complex shapes). We are of the opinion that the description of shape, colours and markings is sufficient. The providing of such information should be at the discretion of the applicant. In addition, as this is a guideline, the wording "must" is not appropriate. The sentence should read: *"A visual description of the appearance of the product (colour, markings, etc.) should be given,…"*	Size should be given because it is an important part of the visual description which is useful to healthcare professionals, e.g. to consider if the product can be easily swallowed. "Must" has been replaced with should throughout the document since it is a guideline which advises on the best or more appropriate way to fulfil an obligation laid down in the community

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
		pharmaceutical legislation.
EACPT	It is appreciated that there is a "must" to visually describe the appearance of the product For clarity and consistency, I propose to use always the verb SHOULD instead of MUST; e.g. *"A visual description of the appearance of the product (colour, markings, etc.) should ~~must~~ be …"*	Comment acknowledged, however must had to be replaced by should because of the status of the document; see above. See above.
EFPIA	Actual size of a tablet is difficult to be measured precisely and therefore will not provide useful information for the physician. The description of shape and markings is sufficient. For the visual description, suggest clarifying wording for the dosage form for the pH and osmolarity attributes is used as per the solid oral dosage form. Proposal to delete this part of the sentence "A visual description of the appearance of the product (colour, markings, etc.) must be given, in a separate paragraph to the standard term, including information ~~on the actual size of a solid oral formulation, or~~, on pH and osmolarity <u>of parenteral dosage forms</u>, as appropriated e.g…."	Size should be given because it is an important part of the visual description which is useful to healthcare professionals, e.g. to consider if the product can be easily swallowed. As suggested, Recommendations on pH and osmolarity have been separated.
MSD	Concern regarding the requirement to add tablet (dosage form) dimension(s) on the SPC as part of the tablet "appearance". It does state "as appropriate". Dimensions are controlled by the tooling used for tablets. However, we have not put this detail in the specification section. When requested for this information (recently, we have been requested to provide this information by a few agencies) we have provided this info but have not added it into our specs. Our release labs do not perform this test/verification. <u>Recommendation:</u> Include "if consistent with" supporting CMC data from product dossier.	Consistency with CMC data should be part of the assessment.
Roche	Information on the actual size of a solid oral formulation. How relevant is this information to the prescriber? Do not you think this is excessive detail? Proposal: remove the size of the tablet	See above
AEFI	Include information on the actual size of a solid oral formulation: "*White, circular flat bevelled-edge tablets <u>of 5 mm</u> marked `100´ on one side*" How relevant is this information to the prescriber?. It seems an excessive detail. Remove the inclusion of the size of the tablet	See above
Pharmaceut-ics LLC	Include instructions on how to measure the size of a solid oral dosage form. The image below shows the instructions for determining size for the purposes of structured product labeling in the USA.	Information acknowledged

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	CDER DATA STANDARDS MANUAL  FDA Data Element Number. Pending. CDER Data Element Number. C-DRG-0928 Data Element Name. SPLSIZE Version Number. 1.0 Description. A characteristic of an oral solid dosage form of a medicinal product, specifying the longest single dimension of the solid dosage form as a physical quantity in the dimension of length (e.g., 3 mm). **Example:** SPLSIZE for a rectangular shaped tablet is the length and SPLSIZE for a round shaped tablet is the diameter. **Constraints:** The length is always in millimeters and should be rounded to the nearest whole millimeter.	
EVM	To extend the paragraph to explain exactly when pH, osmolarity etc… must be included in this paragraph and to define more precisely the meaning of "*as appropriate*"	This will be part of the assessment for each product.

In case of tablets designed with a score line, information should be given on whether or not reproducible dividing of the tablets has been shown. e.g. 'the scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses', 'the tablet can be divided into equal halves'.

Information on pH and osmolarity should be provided, as appropriate.

In case of products to be reconstituted before use, the appearance before reconstitution should be stated in this section. Appearance of the product after reconstitution should be stated in section 4.2 and 6.6.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
MHRA	A mandatory requirement for inclusion of a visual description and dimensions is fully supported and will also be a welcome addition to the patient information leaflet to aid identification.	Comment acknowledged. It will also be transmitted to the QRD group for consideration for the package leaflet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The indication(s) should be stated clearly and concisely and should define the target disease or condition distinguishing between treatment (symptomatic, curative or modifying the evolution or progression of the disease), prevention (primary or secondary) and diagnostic indication. When appropriate it should define the target population especially when restrictions to the patient populations apply.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
ESC	"The indication(s) should be stated clearly and concisely"	Indications depend on data supporting each marketing authorisation applications which have to be reviewed on a case by case basis with appropriate statistical and clinical considerations. Competent authorities balance pro and cons in defining or limiting indications. Information on potential differences in specific subgroups may be better expressed in other sections of the SmPC. See also other ongoing activities on benefit risk considerations
	Limiting further specifications ("especially when restrictions to the population apply") "when appropriate", actually sounds vague, but systematic specifications may expose to the risk of exclusions from treatment of all subgroups whose size was not large enough to allow statistical power for sub-analyses in clinical trials, which may apply to large populations in the real world. Further specifications might be appropriate when there is evidence of marked differences in benefits or risks in specific subgroups, for instance when the point estimates go in different directions, but the 95% the confidence intervals include the point estimate	
	The label should clearly indicate the disease for which it is intended. For drugs acting on the cardiovascular system, the definition of the disease should be made according to those listed in the Guidelines of the European Society of Cardiology, since they are the ones on which cardiologists in Europe base their therapy.	See above
	It is important to state clearly in which patient population the new drug has been shown to be effective, ie if a drug has been tested mainly in male patients, this should be indicated in the SmPC. A sufficient number of females as well as old patients should be included in the study population.	Specific information on special populations is foreseen through the SmPC and could be applicable for informing on potential differences between male and female. Checking that a sufficient number of females have been included in clinical trials is part of the review of each marketing authorisation application. Demographic characteristics of population studied in pivotal trials are described in public assessment reports.
	It must be clear whether the new drug has been tested in a large sample of European patients since most treatments and their response differ between Europe and the rest of the world. Studies conducted solely or mostly in the US and in Asia should not be accepted given the lower standard of medical care, difference in use of drugs and differences in patients as FDA requires to include a sizeable proportion of ethnic minorities that are poorly represented in the EU, and whose response may influence the overall results.	See ICH E5 guideline on Ethnic Factors in the Acceptability of Foreign Clinical Data.

Study endpoints should not normally be included, unless such mention is specified as being appropriate for the indication in CHMP Guidelines. The objective of a prevention indication may be mentioned in general terms only. This should also be done for the target population.

Where results from subsequent studies provide further definition or information on an authorised indication, such information, provided it does not itself constitute a new indication, may be considered for inclusion in section 5.1.

Mandatory conditions of product usage not covered more appropriately in other parts of the SmPC may also be included when relevant, e.g. concomitant dietary measures, lifestyle changes, or other therapy.

~~The indication should state in which age groups the product is indicated~~It should be stated in which age groups the product is indicated, specifying the age limits, e.g. 'X is indicated in <adults><neonates><infants><children> <adolescents> <aged x to y <years, months>>~~from the age of X <months><years > > or up to the age of X <months><years> '~~.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
BfArM	In the current draft it is proposed that the indication states specific age limits. Alternatively, depending on the properties of the agent, it might also be appropriate to state specific weight limits. Add: *"Depending on the properties of the agent, it might also be appropriate to state specific weight limits."*	This information will have to be in section 4.2. In some cases it might also be another classification of the paediatric population, e.g. based on other variables such as gestational age.
TEDDY	According to the Paediatric Regulation, a new medicines/variation should include paediatric references. In particular, a paediatric indication, including all paediatric ages subgroups, could be avoided only if a waiver/deferral has been granted or if results of paediatric studies have demonstrated no paediatric efficacy/safety concerns. Thus, the lack of a paediatric indication should be justified. If the drug is indicated only for the adult population, or for the older paediatric populations, justification should be included	This revision of the SmPC guideline clarifies how to present information in the paediatric population. Public assessment reports provide the ground for the recommendations of the authorisation of a medicine for the therapeutic indications stated in the SmPC. Furthermore, reason for the lack of indication in a paediatric subset has to be described in section 4.2 (see below).
MSD	We recommend that the paediatric indications by age group should be presented in a tabular format for better readability of this section.	Tabular format is suggested in section 4.2.
EVM	Propose to modify the sentence as follows: *"...X is indicated in <adults><neonates><infants><children> <adolescents> from the age of X <months><years > > and/or up to the age of X <months><years> '*	Text harmonised with section 4.2.
Pharmiceut-ics LLC	The concept "indication" is usually understood to represent a sufficient reason for using a product, typically consisting of e elements: an intent of use (e.g. "prophylaxis of") and a target condition for use ("diabetes mellitus"). Additional criteria that further delineate the target population for use (e.g. "in	See rewording above.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	adults" are usually not considered to be part of the indication. The sentence should be changed to read: "It should be stated in which age groups the product is indicated, specifying the age limits, ..."	
EFPIA	The draft revised guideline appears to require that the indication should state in which age groups/limits the product is indicated, without exception, including mention of "indicated in adults". Specific age groups or limits are unlikely to have been established for the indication of many products. Other sections of the SmPC may, however, include advice on use or restrictions in specific age groups (e.g. in 4.2 or 4.4). In such cases, stating that a product is "indicated in adults" may give the false impression that it should not be used in other age groups. By default, there should be no need to specify age groups or limits in the indication. Consistent with the last sentence of the first paragraph of the guidance on section 4.1, specific age groups/limits should only be specified in the indication "when appropriate…especially when restrictions to the patient populations apply." We propose that text from the current version of the guideline should be reinstated into the penultimate paragraph of 4.1. The word 'indicated' in this place may be misleading, as there may be a clinical indication, although the product is not authorized for use in a specific age group. A different terminology is proposed. Amend as follows: *"When the product is authorized for use in a specific age group, such as children/adolescents, the indication should ~~state in which age groups the product is indicated,~~ specifying the age limits where appropriate, e.g. 'X is indicated in ~~<adults>~~<neonates><infants><children> <adolescents> <from the age of X <months><years >> or <up to the age of X <months><years>>'."*	It is important to make clear in which age groups a product is indicated to avoid confusion

If the product's ~~efficacy~~ indication ~~is related to~~ depends a particular genotype~~,~~ or the expression of a gene or a particular phenotype, this should be stated in the indication.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
EACPT	It is appreciated that the relation to a particular genotype, the expression of a gene or a particular phenotype should be stated in the indication.	Comment acknowledged
MSD	"If the product's efficacy is related to a particular	See clarification of the

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	genotype, the expression of a gene or a particular phenotype, this should be stated in the indication." Recommendation: This information should be presented in the clinical study section. In the indication section, it should be optional and inclusion of the wording "if appropriate" is recommended.	wording.
Roche	Reference to other relevant sections of the SmPC should be provided to avoid a lot of information to be included in the indication section. *"If the product's efficacy is related to a particular genotype, the expression of a gene or a particular phenotype, this should be briefly stated in the indication with appropriate reference to section 4.2 and/or 5.1 where applicable."* It is not possible to define a "particular phenotype" unless we are talking here about a pure population, which is a particular genotype. If genomic analysis is done, we are at the genotype level. If "particular phenotype" will be remain in the text, may be better to make direct reference to a given ethnic group. Delete "particular phenotype" or specify particular ethnic group if needed.	See clarification of the wording Differences may also be linked to a various particular (clinical or laboratory) phenotypes and not only to ethnic group.
ESC	All sections include specific remarks on genotype or polimorphisms. This is right, but this kind of information should be used parsimoniously and judiciously, when there are strong evidence and clear clinical implications. The main reasons are the frequent inconsistency of such data in the literature and the infrequent availability on individual users to the health care professionals	Those data will be presented in the SmPC only after validation by competent authorities and if considered relevant for the safe and effective use of a medicine by healthcare professionals.
BfArM	Add; *"If the product's efficacy is limited related to a specific pharmacokinetic characteristic (e.g. prolonged onset of efficacy in an acute indication) this should be stated in the indication."* E.g. products for the symptomatic treatment of OA may have a prolonged or modified galenic formulation thus are not appropriate for the initiation of treatment (pain relief), this information should be added/included in section 4.1.	The indication should clearly identify the target disease and when necessary the target population, based on the pharmacodynamic and pharmacokinetic properties of the disease. Conditions in which the product will not be suitable should be better described in other sections e.g. 4.3 or 4.4.
ESNO	Add less specific, but nevertheless frequent use for pharmacokinetic reasons (i.e. Clonidine for strengthening regional anaesthetics effects in epidural etc…)	New indications are granted following assessment of competent authority of an application by the marketing authorisation holder according to scientific requirements
MEDEV /ESIP	*"The indication(s) should be stated clearly and concisely and should define the target disease or condition distinguishing between treatment (symptomatic, curative or modifying the evolution or*	This proposal could be better considered in a specific project looking at the whole SmPC to facilitate its use in

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	progression of the disease), prevention (primary or secondary) and diagnostic indication." PROPOSAL: An international code of the disease or disorder according to the ICD-10 (international statistical classification of diseases and related health problems, WHO) should be included. This would simplify and unify databases used for the informational support for electronic prescribing, analyses etc. We are aware that in some clinical fields (for instance oncology) some medicines have very specific indications that are based on TNM or other classifications and that some medicines are indicated for first, second or third line treatment, which is impossible to define by ICD codes. Anyway, coding of basic indications would significantly increase possibilities for informational support and especially for evaluation of data.	electronic tools.

4.2 Posology and method of administration

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
EASD	EASD supports suggested changes to posology and administration, and welcomes a clear step-by-step guide for the introduction of the agent, especially if it is to be added to one or more concurrent therapies. Similarly straightforward guidance for missed doses and intercurrent illnesses would be helpful. Where initiation of a drug in a particular sub-group can be complex or problematic, it may be useful to include a reminder to consider referral to a specialist.	Comments acknowledged and consistent with the guideline.
Roche	The dosage for specific target population, eg paediatrics, is given twice; once right at the beginning of the section ("posology") and then under the specific sub-heading "paediatrics". List specific dosage/administration instructions only under the sub-heading "paediatrics"; this way, the information is easier to retrieve (this subheading appears in many sections, healthcare professional can go directly to this subheading to get required information)	Agreed; first reference to specific target population deleted at the beginning of the section to avoid confusion. See below.
EFPIA	We recommend including paediatric population in other special populations. Advice should be provided on whether the order of the population categories presented in the guidance is fixed or whether it can be dictated by relative population importance case-by-case e.g. move "paediatric population" category before elderly, renal impairment etc.	The order of the specific population categories is not fixed and can be modified to highlight important information.

In case of restricted medical prescription, this section should be started by specifying the conditions.

ORGANISA-TION	COMMENT(S)	OUTCOME/CONCLUSION
ESC	In cardiology no oral drugs should be prescribed by the cardiologists only, except for few that for a very high cost, special /rare indications or many severe side effects should be prescribed and administered by hospital cardiologists only.	Information on where restriction of prescription may be acceptable is available in the EMEA Guideline on Legal Status for the supply to the patient of centrally authorised medicinal products (EMEA/186279/2006)

In case of specific safety ~~or monitoring~~ need, any recommended restriction to a particular setting ~~type of clinical unit~~ should also be stated (e.g. "*restricted to hospital use only*" or "*appropriate resuscitation equipment should be availa*ble").

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
EFPIA	The statement on safety or monitoring need is unclear. Firstly, names of clinical unit may vary between Member States. Secondly, does it refer to a need at treatment initiation only? We suggest include examples in parenthesis after this sentence; Please reword the statement as follows: ~~In case of~~ If a specific safety or monitoring need at treatment initiation justifies ~~any recommended~~ the restriction of the administration to a particular type of clinical unit, it should also be stated (e.g. drug to be administered by a cardiovascular specialist)..	Wording clarified. See above.
EVM	"In case of specific safety or monitoring need, any recommended restriction to a particular type of clinical unit should also be stated". It seems inappropriate to specify warning or safety in this section, rather than in section 4.4 or 4.8. Or at least cross-reference to these sections should be stated.	As already foreseen (see below), it is relevant to *"advice on preventive measures to avoid certain adverse drug reactions with cross-reference to section 4.4"*
MEB	It is not clear what is meant with 'clinical unit'. A explanation should be added.	Wording clarified. See above.
MSD	"In case of specific safety or monitoring need, any recommended restriction to a particular type of clinical unit should also be stated." Recommendation: To apply this statement per the local health authorities rather than generalizing across EU.	Wording clarified. See above.

Posology

The dosage ~~has to~~should be clearly specified for each method/route of administration~~,~~ and for each indication ~~and for each specific target population (e.g. age group)~~, as appropriate.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
AESGP	For clarification purposes, we propose the following wording: *"…. for each specific target population, if appropriate (e.g. age groups as indicated in chapter 4.1, Therapeutic indications)."*	Wording simplified considering that special populations are addressed later.
EFPIA	The proposal is to specify dosage "…for each indication and for each target population (e.g. age group), as appropriate." This may be done best in a table. Usually the target population is all patients with a disease, even if they have renal/hepatic impairment, are taking medicines, etc. There should not be a need to repeat all this information in the special populations section further on. Clarify that when adjustments in posology are recommended for a particular target population, these should be indicated. If no adjustments are recommended, there should be no need to duplicate posology information.	It has been made clearer at the beginning of the guideline, under "General principles" that each section of the SmPC should first inform on the characteristics applying to the core population to whom the medicine is indicated followed - when necessary – by specific information for any relevant special population. See also above.

Where appropriate, a reference to official recommendations should be made (e.g. for primary vaccination and antibiotics as well as for booster dose).

~~Specify d~~Dose recommendations ~~per dose interval~~ (e.g. mg, mg/kg, mg/m^2) should be specified per dose interval for each category where appropriate (specify age/weight/body surface ~~ranges~~ area of subsets of the population as appropriate). Frequency of ~~intake~~ dosing should be expressed using time units (e.g. once or twice daily or every 6 hour) and, to avoid confusion, abbreviations e.g. OD or BID should not be used ~~to avoid confusion~~.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
Roche	The SmPC is addressed to Healthcare professionals, so abbreviations, such as OD or BID, can't be misunderstood. These abbreviations are currently extensively used in all SmPCs.	Abbreviations have a higher risk of misinterpretation and should be avoided where possible.

Where appropriate, the following points should be addressed:

- the maximum recommended single, daily and/or total dose,
- the need for dose titration,
- the normal duration of use and any restrictions on duration and, if relevant, the need for tapering off, or advice on discontinuation,
- advice on action to be taken if one or more dose(s) is (are) missed, ~~and~~ or e.g. in case of vomiting (The advice should be as specific as possible as possible, taking into consideration the recommended frequency of dosing and relevant pharmacokinetic data)

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
Roche	Advice is to be included in case compound has possibly not been absorbed due to vomiting; absorption could also be diminished by diarrhea- advice on action…is (are) missed, and in case of vomiting or diarrhea" Any advice on what to do in terms of a repeat dose in case of vomiting should make clear that vomiting is only relevant in relation to oral medication. Suggest change to '…and where oral administration may have been expelled due to vomiting'	It is recognised that in some cases advice on action to be taken in case of diarrhoea would be important. See above proposal for vomiting as example. Relation with oral medication is obvious for addressees to this guideline.
BfArM	The recommendations should be made as specific as possible, taking into consideration the pharmacokinetic profile of the agent (e.g. "Take the forgotten dose, if you notice within X hours. If you notice later,..."). As an alternative, a general recommendation can be added following the whole list of bullet points here reminding that any advice should be given as specific as possible considering the properties and pharmacokinetic profile of the active substance. advice as specific as possible on action to be taken if one or more dose(s) is (are) missed, considering the pharmacokinetic profile of the agent., and in case of vomiting	See above revised wording
MHRA, Vigilance and Risk Management of Medicines Division	The draft guidance states that where possible, the SPC should address "advice on action to be taken if one or more dose(s) is (are) missed, and in case of vomiting". Additionally, the advice could: specify the delay after which a dose is considered "missed"; take into account the time between the dos e and the vomiting episode; if vomiting occurs as a result of taking the medicine, provide advice on how vomiting can be prevented	Taken into account; see above revised wording. Management of vomiting: issue addressed in the next bullet point.
AESGP	'Advice to be given in case of vomiting'. Data to support guidance on this may be difficult to obtain.	See above

- advice on preventive measures to avoid certain adverse drug reactions (e.g. administration of antiemetics) with cross-reference to section 4.4,
- the intake of the product in relation to drink and food intake, together with a cross-reference to section 4.5 in case of specific interaction e.g. with alcohol, grapefruit or milk,

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
AESGP	The reference to taking with food and drink should be qualified. Does this also include interactions such as relation to pharmacodynamic effects e.g. alcohol or pharmacokinetics e.g. grapefruit juice. Guidance should be given as to whether, if information is included in this part, it should also be repeated in the interactions section. Or should it be primarily in the Interaction section with a cross reference?	Agreed; see above

- advice regarding repeat use, with any information on intervals to be observed between courses of treatment, as appropriate,
- interactions requiring specific dose adjustments with cross-reference to other appropriate sections of the SmPC (e.g. 4.4, 4.5, 4.8, 5.1, 5.2), and
- ~~Different dose recommendations based on genotype.~~it may also be relevant to recommend not to prematurely discontinue a treatment in case of specific non-serious adverse reaction(s) that are frequent but transient or manageable with dose-titration.

Where relevant to the particular product, the following should appear 'The potency of this medicinal product is expressed in <invented name> units. These units are not interchangeable with the units used to express the potency of other <active substance name> preparations'.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
CZ QRD	"Different recommendations based on genotype" is already mentioned below in the Special populations subsection. Suggestion: mention it once, in the Special populations subsection.	Agreed (see deletion above)
Roche	Based on genotype. The genomic tests have to be explicitly explained and even proteomic tests to better know the expression level of the protein in order to better adapt the dose to a given patient. Genomic tests to perform have to be explicitly mentioned. Cross-refer to sections 4.3, 4.4 and 4.5 if any particular genotype suggest it (i.e., CYP subunits).	Comment taken into account (see below)
EFPIA	"Different dose recommendations based on genotype" should be mentioned under Posology header, but it is also mentioned under the Special population header (4th bullet point) "Patients with a particular genotype". This is repetitive. It is proposed to mention "Patients with a particular genotype" only once and under the header Special Populations.	Agreed (see deletion above)

Special populations

Dosage adjustments or other posology related information in specific patient groups should be stated~~,~~ where necessary, in well-definedidentified sub-sections ordered by ~~by~~ importance, e.g. regarding:

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
Roche	Sub-sections ordered by importance may be difficult to define based on medical judgement. In addition, it will not be clear to a physician that the order is of medical relevance. Suggestion to keep a standard order in this section. Consider optional header for other special populations.	There is no single standard order which will be appropriate to all medicines. In any case, sub-headings should help prescriber to identify the necessary information. It may be more important to firstly describe a population where a dose-adjustment has been identified than a population for which data are missing but for whom there is no particular safety concern.

- ~~E~~elderly population; it should be made clear whether or not any dosage adjustment is necessary in any subsets of the elderly population, with cross-reference to other sections providing information in elderly, e.g. 4.4, 4.5, 4.8 or 5.2.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
Roche	Among other sections providing information in elderly which are cross-referenced, section 4.4 could also be considered. In section 4.4, information on precaution for use specific to the elderly population might also be included. With cross-reference to other sections providing information in elderly, e.g. 4.4, 4.5, 4.8 or 5.2	Examples are not expected to be exhaustive. Even if a cross-reference to section 4.4 could be acceptable in some cases, it should not be encouraged especially if there is already information on dosage adjustment in section 4.2 and supportive data in other sections.
AEFI	In section 4.4, information on precautions for use related to elderly population might also be included. Therefore, section 4.4 could also be included in the cross-reference together with other sections. Mention also section 4.4. "With cross-reference to other sections providing information in elderly, e.g. 4.4, 4.5, 4.8 or 5.2".	See above.
EVM	The age limit for "elderly population" should be clarified.	See ICH guideline.

- renal impairment; the dose recommendation should relate as precisely as possible to the cut-off values for biochemical markers of renal impairment in clinical studies and to the results of these studies;

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
BfArM	The most appropriate biochemical marker is the creatinine clearance. The wording should support to adjust dose recommendations in relation to the decrease of this biochemical marker. renal impairment; the dose recommendation should relate as precisely as possible to the cut-off values for biochemical markers of renal impairment in clinical studies and to the results of these studies, preferably expressed as creatinine clearance;	This recommendation should be read in conjunction with the guideline on pharmacokinetics in patients with renal impairment. (CHMP/EWP/225/02).

- hepatic impairment, specified according to the patients included in studies, for instance 'alcohol-related cirrhosis' and the definitions used in the studies, for instance Child-Pugh score/grade of the patients;
- patients with a particular genotype; with cross-reference to other relevant sections for further detailed as appropriate,
- ~~overweight patients or o~~Other relevant special population (e.g. patients with other concomitant disease or overweight patients).

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
Roche	Concomitant disease. Cross-refer to section 4.3	Information in relation to concomitant disease may not systematically lead to a contraindication.
MSD	This (i.e., overweight patients) is not a separate patient population, and subject to individual interpretation. Recommendation: Should not accept. However, if body weight needs to be taken into consideration that should be expressed as dose/body weight (e.g. mg/kg).	See rewording
AESGP	Information for overweight patients may require additional studies or evaluation of data. This should only be applicable for new MA applications and if seen as relevant.	See above
EFPIA	Relevant differences between ethnic groups are to be considered here. Please add. "Dose recommendations in ethnic groups if they are different." The criteria for the special populations should be defined (e.g. what is overweight, which concomitant medication). Furthermore, it should be clearly stated that the information on special populations should only be included if available. (The need to study (or not) certain populations is included in other guidance) Please clarify how to order the various special populations by importance.	The guideline does not exclude this possibility. Examples cannot be exhaustive. Requested clarifications are beyond the scope of this guideline. See also previous answer to the comment on the order of special populations.

Advice relevant for dosage adjustment e.g. from monitoring of clinical symptoms and signs, and/or laboratory investigations, including blood concentrations of the medicinal product should be mentioned when appropriate with cross-reference to other section where appropriate.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
EASD	**EASD** concurs that some quantitative guidance should be offered where practical to indicate extents of renal and liver impairment, since interpretations of qualitative advice are quite variable. While Child-Pugh scores may be appropriate for decisions about use of some agents, markers of less severe liver impairment such as liver enzymes may be appropriate and acceptable in some situations.	Comments acknowledged. SmPC guideline to be read in conjunction with CHMP guidelines on renal or hepatic impairment.
IPFA	Advice relevant for dosage adjustment e.g. from monitoring of clinical symptoms *and dosage adjustment due to toxicity* and signs, and/or laboratory investigations, including blood concentrations of the medicinal product should be mentioned when appropriate with cross-reference to other section where appropriate	Not necessary
MHRA, Vigilance and Risk Management of Medicines Division	Age and weight ranges: Where age and/or weight ranges are stated, these must be expressed in a form that is unambiguous and does not contain any gaps.	See above

Paediatric population

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
EFPIA	Consistent terminology is recommended. As the subsection is also required in places where the information is not necessarily related to patients, consistent use of the term 'paediatric population' is recommended. Furthermore, for some drugs (that are used to treat, for example, Parkinson's Disease) this section would be irrelevant. The specific sub-section 'paediatric ~~patients'~~ population should always be included. Add another statement to indicate that this section may be irrelevant in certain circumstances, i.e., when the product has been granted a waiver by the PDCO.	Agreed. See below regarding the need for the subsection

The specific sub-section 'paediatric ~~patients' ~~population' should always be included and the information given should cover all subsets of the paediatric population, using a combination of the possible situations presented below as appropriate.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
TEDDY	In principle, paediatric dosages should not be recommended in patients for which the medicinal is not indicated. However, this provision could favour the off-label use in the whole paediatric population or in subgroups. In alternative, we could change the first sentence as follow: "If the product is indicated in the paediatric population, the specific sub-section 'paediatric patients' should always be included". If the product is not indicated in paediatric population or in some paediatric subpopulations, the provision of paediatric dosages in the sections 4.2 should be justified. The risks that could derive from an 'off-label' use in these groups of patients should also be underlined.	It is acknowledged that posology in a specific population should not be recommended in absence of an indication. When the product is not indicated in children, a general statement informs on which data are available.
AESGP	For clarification purposes, we propose the wording: *"If the product is indicated in paediatric population, the specific sub-section 'paediatric patients' should always be included. Information should be given for the different …"*	*See above*
EVM	*"The specific sub-section "paediatric patients" should always be included"* No sub-section of paediatric population is needed when the product is only indicated in a paediatric population. Propose to modify as follows: *The specific sub-section "paediatric patients" should always be included (unless irrelevant)*	Acknowledged but cases where stating "unless irrelevant" without further explanation would be confusing.

If the product is indicated in the paediatric population, ~~information~~posology recommendations should be given for each of the ~~different~~ relevant subsets. The age limits should reflect the benefit-risk assessment of the available documentation for each subset.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
MSD	The sentence "The age limits should reflect the benefit-risk assessment of the available documentation for each subset." may not be clear to prescribers. Please rephrase: "The age limits should reflect the clinical studies or other data for each subset."	The sentence is not addressed to prescribers but to applicants and regulators to ensure that the SmPC reflects available data.

If the posology is the same in adults and children, then a statement to this effect is sufficient; the posology does not need to be repeated.

Dose recommendations (e.g. mg, mg/kg, mg/m2) should be specified per dose interval for the paediatric subsets where the product is indicated. Different subsets may require different dosing information. If necessary, recommendations in preterm newborns should be presented taking into account the more appropriate age e.g. gestational age or the ~~post-conceptional age~~post-menstrual age.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
MHRA, Vigilance and Risk Management of Medicines Division	Consideration should be given to the way the age of a preterm or a premature infant is expressed. The draft guidance mentions *gestational age* and *post-conceptual age*; many consider that the appropriate concept to use is post-menstrual age.	See change above.

Depending on the subset, the clinical data and available formulations, the dose will be expressed according to weight or body surface area, e.g. "*children aged 2-4 years, 1 mg/kg bodyweight twice a day*".

When appropriate information on timing of intake of the product should consider children's daily life, e.g. school or sleep.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
Pharmasy-mbiosis Ltd's	Pharmasymbiosis Ltd's proposed rewording: "When providing information on timing of the use of a product in children, consideration should be gvien to their daily routines of meals, sleep and school"	Consistent with wording above.
AESGP	The statement *"Information on timing of intake of the product should consider children daily life, e.g. school or sleep"* is a bit unclear. How does this information need to be interpreted and used? Does this mean a product causing drowsiness should not be taken when a child is at school? Or that intake with lunch/ at lunch time may be difficult if a product needs to be refrigerated for example? Only general guidance could at the most be provided here in light of the fact that e.g. school schedules are different throughout Europe and guidance in one country may not be true for all. We would propose that this is restricted to the most serious cases when the intake intervals have to be strictly respected. In the other cases, general guidance should be provided only if possible/appropriate.	Agreed *"When appropriate"* has been added at the beginning of the sentence
EFPIA	Children's daily life may in some cases be difficult to take into account and may also vary between Member States. Information on timing of intake of the product should consider children daily life if possible, e.g. school or sleep.	See above

~~In exceptional cases w~~Where a product is indicated in children ~~the "adult" formulation (or an "older age group" formulation) of the medicinal product includes an indication and a posology for use in children, or includes, at least, a posology for use in children,~~ and ~~where~~ no adequate paediatric formulation can be developed ~~(based on duly justified scientific grounds)~~, detailed instructions on how to obtain an extemporaneous preparation shall be included in section 6.6 with a cross-reference in section 4.2.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
Pharmasy-mbiosis Ltd's	It is not normal practice to provide information on how extemporaneous preparation, in an SPC as such formulations are largely without marketing authorisations and as such cannot be mentioned in the SPC	Recommendation clarified; see revised wording.
MPA	The following paragraph should be revised "In exceptional cases where ***a product is indicated in children*** ~~the "adult" formulation (or an "older age group" formulation) of the medicinal product includes an indication and a posology for use in children, or includes, at least, a posology for use in children,~~ and where no adequate paediatric formulation can be developed (based on duly justified scientific grounds), detailed instructions to obtain an extemporaneous preparation shall be included in section 6.6 with a cross-reference in section 4.2." The change is made in order to minimise repetitive information and extensive text.	Agreed
MHRA, Vigilance and Risk Management of Medicines Division	(see also comments on Section 6.6) Inclusion of instructions for extemporaneous preparation should be severely restricted to the most exceptional cases e.g. where necessary to ensure that a particular medicine can be given to children in the event of a flu pandemic. We are concerned that the phrase 'exceptional' will allow MA holders to avoid developing formulations which are suitable for children if it is interpreted too widely – in contrast to the stated objectives of the EU Paediatric Regulation. Consideration should be given to strengthening the wording of this paragraph both here and in Section 6.6 to make the nature of the exceptional case clearer.	See above
EFPIA	We believe that these judgements are beyond the scope of this guidance. This section should be limited to an expectation that 'for an extemporaneous preparation, detailed instructions will be provided in section 6.6 with a cross-reference in section 4.2'	See above

Doses and method of administration in the various subsets may be presented in a tabulated format.

If there is no indication for the product in ~~any~~some or all subsets of the paediatric population, no posology recommendation can be made, but available information should be summarised using the following standard statements ~~are suggested~~ (one or combination of several as appropriate):

- The <safety> <and> <efficacy> of X in children aged x to y <months, years>*<or any other relevant subsets e.g. weight, pubertal age, gender>* <has><have> not <yet> been established.

  One of the following statements should be added:

  – <No data are available>.

  or

  – <Currently available data are described in section <4.8><5.1><5.2> but no recommendation on a posology can be made >~~. <No posology can be recommended.>~~

- X ~~<~~should not be used~~>~~ in children aged x to y <years, months>><*or any other relevant subsets e.g. weight, pubertal age, gender*> because of <*safety*> ~~*or*~~ <*efficacy concern(s) to be ~~explained~~stated*~~>~~ with cross-reference to sections detailing data (e.g. 4.8 or 5.1)>.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
MSD	We recommend that the safety and/or efficacy concerns should only be "stated" in brief and not "explained" in detail as this is done in another sections. X should not be used in children aged x to y years, months because safety or efficacy concern(s) to be stated with cross reference to section detailing data(e.g.4.8).	Agreed
EFPIA	Posology, Paediatric population – 'The <safety><and><efficacy of X in children aged x to y <month, years>...<No posology can be recommended>. This is an unclear way of saying that use in this population is not recommended – which is what it used to say. Any other statement might be seen to be encouraging off-label use. Suggest this statement concludes <Therefore use in this population is not recommended.>	"*<use is not recommended.>*" appears to be inconsistently interpreted. Description of factual information or clear recommendation such as "*should not be used*" is therefore preferred.

- There is no relevant ~~indication for~~ use of X in <the paediatric population><in children aged x to y><years, months>><*or any other relevant subsets e.g. weight, pubertal age, gender*> in the indication(s) <specify indication(s)>.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
MEB	The sentence *"There is no relevant indication …"* should be deleted. This sentence does not add useful information to the information in the SPC. - The healthcare professionals know when an indication is not relevant for children, e.g. erectile dysfunction, hormone replacement therapy in post menopausal women. - In some cases the product needs to be used in children off-label, if there is no approved product for a specific indication in children. This sentence will avoid off-label use. - Usually the indications the product should not be used for are not mentioned in the SPC. If necessary, the other sentences.	Need to be kept to ensure completeness of the information. Wording has been simplified. Recommendations in these subsections have also been slightly reworded to make clear that no posology recommendation can be made in absence of indication in the concerned population.
Pharmasy-mbiosis Ltd:	The word 'relevant' is unnecessary as there is no such thing as irrelevant indications	See proposed rewording

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
Roche	Which statement should be included for class waivers? ("There is no relevant indication…") "<Indication> does not occur/occurs only very rarely in the paediatric population." Or: "The authorised indication does not occur in the paediatric population."	The option proposed in the bullet point above.

- X is contraindicated in children aged x to y <years, months><*or any other relevant subsets e.g. weight, pubertal age, gender*> <in the indication…> (cross-reference to section 4.3).

~~In case only part of the strengths or pharmaceutical forms of a medicinal product is indicated in a subset of the population, section 4.2 of the the SmPC of other strengths or pharmaceutical forms may cross-refer to it or them.~~

If there are more appropriate strength(s) and/or pharmaceutical form(s) for administration in some or all subsets of the paediatric population (e.g. oral solution for infants), these can be mentioned in section 4.2 of the SmPC of the less appropriate one(s).

E.g.: ~~INN/strength/pharmaceutical form is not indicated in children aged x to y <years, months>, in whom the following formulation should be used: INN/strength bis/pharmaceutical form bis~~Other pharmaceutical forms/strengths may be more appropriate for administration to this population.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
Roche	If there is a specific pediatric formulation, I believe it would be sufficient to cross-refer to that particular SmPC in which detailed posology will be described. From the draft is seems that all details need to be included here for any formulation. There is a sentence included this effect at the end of this sub-section, however should be more clear in the beginning of the section. Move sentence currently at the end of this sub-section to beginning and add examples, e.g. Proposed sentence to be included in the SmPC of the "adult" formulation: *For children unable to take this formulation, XXX [include name of adult formulation] may be administered) (see Summary of Product Characteristics for XXX for recommended posology)* Proposed sentence to be included in the SmPC of the pediatric formulation: *XXX [include name of adult formulation] are recommended for adults and older children (if applicable) (see Summary of Product Characteristics for XXX for recommended posology).*	Comment taken into account through the addition of an example (see above)

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
AESGP	Cross-referencing between SmPCs of different pharmaceutical forms might also be valuable for adult indications in specific situations. Guidance on the acceptability of such cross-referencing would be very helpful.	It is acknowledged that cross-referencing could also be relevant for adult patients who may have difficulty in swallowing. However, development of further guidance on such cross-referencing would require a specific reflection

Method of administration

Any special precautions related to the manipulation or administration of the product (e.g. cytotoxic products) by healthcare professionals (including pregnant healthcare professionals), the patient or carers should be mentioned here under a specific sub-heading (*<Precaution to be taken before manipulating or administering the product>*), with a cross-reference to section 6.6 (or 12).

The route of administration and ~~short~~ concise relevant instruction for correct administration and use should be given here. Information on instructions for preparation or reconstitution should be placed in section 6.6 'Special precautions for disposal of a used medicinal product and other handling of the product' (or in section 12 if appropriate) and cross-referenced here.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
MEDEV /ESIP	It should be emphasized in the guideline that in case of route of administration the standard terms must be used like in case of the denomination of pharmaceutical forms.	Use of consistent medical terminology throughout the SmPC is recommended in the general principles. In the case of the route of administration the EDQM standard terms are usually appropriate. (See QRD template)
MHRA, Vigilance and Risk Management of Medicines Division	If children are not likely to find an oral product particularly acceptable (e.g. because of taste, consistency or colour), then advice should be given on how the child might be helped to take it. This might include use of foods, liquids or other substances that mask the taste or otherwise improve acceptability. Common foods and drinks that do not adversely affect the medicine should be listed.	Comment taken into account; see revised sentence below

When supportive data are available, information on alternative method(s) ~~of~~ to facilitate administration or acceptability should be given as explicitly as possible (e.g. possibility of crushing tablet, cutting tablet or transdermal patch, pulverising tablet, opening capsules, mixing with food, dissolution in drinks – specifying if a proportion of the dose can be given) particularly for administration via ~~a~~ feeding tubes.

Any specific recommendation for use related to the pharmaceutical form should be explained, e.g.:

- "the coated tablet should not be chewed because of <bad taste>,

- “the enteric-coated tablet should not be crushed because coating prevents <pH sensitive degradation><irritant effects> on the gut”,
- “the coated tablet should not be broken because the coating is intended to ensure a prolonged release (see 5.2)”.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
EFPIA	Certain information presented in the posology section, such as the intake of the medicine with food or drink for an oral dosage form may also be appropriate in this section. The exact relative scope of each section needs better clarification.	Information on intake with food in this section applies to situations where alternative methods to facilitate intake are available.

For parenteral formulations, information on the rate or speed of injection or infusion should be ~~given~~provided.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
ESNO	In mode of administration, need for precising the speed for IV administration (i.e. crash, > 1mn, > 10mn etc…)	Above statement clarified
Roche	Could this be moved up, ie could this section precede the special populations. Proposed order of subheadings -Posology -Method of administration -Paediatric population -(Other) Special populations	It would be confusing to describe the method of administration between different posology recommendations
AESGP	For the dosage recommendations of herbal medicinal products, we would like to suggest including the analytical method the assay has been performed with. In many cases new methods are developed by the European Pharmacopoeia leading to results different from those obtained with established methods. For this reason it is important to know which method has been used.	Outside the scope of this section.
-	-	Statement below added upon PDCO recommendation

For parenteral formulations - in children, especially newborns in whom quite often fluids have to be restricted - it would be useful to have information on maximal concentration that can be safely administered (e.g. "no more than X mg of Y/ml of solution").

4.3 Contraindications

Situations where the medicinal product must not be given for safety reasons, i.e. contraindications, are the subject of this section. Such circumstances could include a particular clinical diagnosis, concomitant diseases, demographic factors (e.g. gender, age) or predispositions (e.g. metabolic or

immunological factors, a particular genotype and prior adverse reactions to the medicine or class of medicines). The situations ~~must~~ should be unambiguously, comprehensively and clearly outlined.

Other medicines or classes of medicine, which must not be used concomitantly or consecutively should be stated, based on either data or strong theoretical reasons. If applicable a cross-reference to section 4.5 should be made.

In general, patient populations not studied in the clinical trial programme should be mentioned in section 4.4 and not in this section unless a safety issue can be predicted (e.g. use of renally eliminated substances with narrow therapeutic margin in renal failure patients). If, however, patients have been excluded from studies due to a contraindication on grounds of safety, they should be mentioned in this section. If applicable a cross-reference to section 4.4~~5~~ should be made.

Only if pregnancy or breastfeeding is ~~strictly~~ contraindicated, should it be mentioned here. In section 4.6, a cross-reference should be made and further background information provided.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
MHRA	Suggest that breast-feeding is included as well as pregnancy in the 4th paragraph. "Only if pregnancy and breast-feeding are ~~is~~ strictly contraindicated " etc.	Agreed; see change above
Pharmasy-mbiosis Ltd:	Strictly contraindicated suggests that there are grades of contraindication. Consider deletion of the word 'strictly'	Agreed *"strictly"* has also been deleted to avoid confusion

Hypersensitivity to the active substance or to any of the excipients or residues from the manufacturing process should be included, as well as any contraindication arising from the presence of certain excipients (see *Guideline on excipients in the label and package leaflet of medicinal products for Human Use*).

For herbal medicinal products, hypersensitivity extended to other plants of the same family or to other parts of the same plant should be labelled as a contraindication, where applicable.

Lack of data alone ~~must~~should not lead to a contra-indication. Where for safety reasons, the product should be contraindicated in a specific population, e.g. paediatric or a subset of the paediatric population, it should appear in this section with a cross-reference to the section giving detailed information on the safety issue. A contra-indication in the paediatric population should be listed without a sub-heading.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
MHRA **Vigilance and Risk Management of Medicines Division**	Consideration should be given to including a separate sub-heading listing contraindications specific to children. This would ensure consistency throughout the SPC and avoid the assumption that there are no contraindications in children because there is not a heading in this section, unlike other sections of the SPC	This section is expected and is used to present clear and unambiguous situation(s) where the product is contraindicated. Addition of a sub-heading would probably hamper its readability. Furthermore, a sub-section "Paediatric population" is not expected for each section.

4.4 Special warnings and precautions for use

The order of warnings and precautions should in principle be determined by the importance of the safety information provided.

The exact content of this section will be different for each product and the therapeutic conditions it is intended to treat. It is however suggested that the following items should be included where relevant to the specific product.

Information on a specific risk should be given in section 4.4 only when the risk leads to a precaution for use or when healthcare professionals have to be warned on this risk. Patient groups in which use of the medicinal product is contraindicated should be mentioned in section 4.3 only and not to be repeated here.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
ESC	Reader categories of this section are expected to be: a) prescribers, b) users, c) both when looking for specific effects usually concerning safety. Provided that contraindications and adverse undesired effects are reported in Section 4.3 and 4.8 respectively, in order to be largely used and useful for many, this section should be simple and relatively short or composed by subsections with different evidence (by editing) according to their relevance. Whenever possible, this section should indicate sources of more complete information. The bullets 3-6 dealing with adverse reactions should be reported in the Section 4.8. Only the adverse reactions that can be prevented by precautions or can be identified by early symptoms of which both physicians and patients should be aware of should be reported here. Vice versa, the non-serious adverse reactions that are frequent in the beginning of the treatment, may disappear with its continuation, but may lead to early discontinuation of a drug might be reported in this Section instead of (or in parallel with) the Section of Undesirable Effects (4.8a).	Acknowledging these comments, the following principle has been added at the beginning of this section: *"Information on a specific risk should be given in section 4.4 only when the risk leads to a precaution for use or when healthcare professionals have to be warned on this risk."* The proposal related to the risk of early discontinuation has been added to section 4.2 as follows: *"it may also be relevant to recommend not to prematurely discontinue a treatment in case of specific non-serious adverse reaction(s) that are frequent but transient or manageable with dose-titration."*.
MSD	Bullets 2, 3 and 4 : Please delete these bullets as the information is redundant with information provided in section 4.8 in an overview table	See above
Pharmiceut-ics LLC	General comments: 1.The guideline has never been very clear in describing what makes safety information qualify to be included in this section. The guidance states that "serious adverse reactions to which the prescriber needs to be alert" should be included. Are these all serious adverse reactions or a subset? Including only a subset appears to be established labeling practice. In addition to such (which?) serious reactions, the guideline (including the revised draft) appears to require that an otherwise not "warning-worthy" undesirable effect is discussed in this section solely because it might occur only in, e.g., men or because it	See above

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	might be more common in men (see current guideline or bullet points 2 and 3 of the draft). This could, for example, mean a discussion of all gender-specific effects in section 4.4 (which is clearly not current labeling practice). Is this really what the guideline intends to achieve? Or is it considered implied (albeit not stated at all) that undesirable effects must have a certain, higher degree of clinical relevance to be included in 4.4. It is, of course, not absolutely necessary to provide further clarification on this section's relevance-threshold for undesirable effects. It is possible to allowing a "labeling tradition" to evolve and to decide which undesirable effects to include in a particular product's section 4.4 on a case-by-case basis, guided by the labeling of similar products and common sense. On the other hand, authors of labeling might appreciate more extensive and clear guidance, in particular if such guidance is consistent with guidance provided in the US. US draft guidance defines that an undesirable effect should be included in WARNINGS AND PRECAUTIONS if it is "serious or otherwise clinically significant". FDA provides examples that explain the concept "otherwise clinically significant" and lists a number of additional relevance factors to be taken into account when deciding which effects to include. These other factors include the magnitude of benefit and the frequency of the undesirable effects. Agreeing among regulatory authorities and other stakeholders on general rules for including undesirable effects in a warnings and precautions section could lead to increased global labeling congruence.	

The following should be described:

- The conditions in which the use of the medicinal product could be acceptable, provided that special conditions for use are fulfilled. In particular, specific risk minimisation measures requested as part of a Risk Management Plan to ensure safe and effective use should be described in this section. (*For example; "Liver function should be monitored before initiation of treatment and monthly thereafter", "Patients should be advised to immediately report any symptoms of depression and/or suicidal ideation", "Women of childbearing potential should use contraception", ...)*

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
EFPIA	It should be clarified that from the measures discussed in the Risk Management Plan only a short description is needed of those which: • refer to data driven 'identified risks' (not potential risks) • the physician has to consider for the treatment of the individual patient • Impact on the content of the SmPC Not all the information presented in the RMP is relevant for the SmPC and specific direct reference to the RMP in the SmPC must not be made	As clarified above, it is not expected to make direct reference to the RMP but to ensure that healthcare professionals are informed on specific risk minimisation measures identified in a RMP.
MEB	In order to avoid confusion we propose to add the words 'risk minimisation'.	Agreed. See above change
AstraZeneca	Our second signficant concern is around section 4.4, the inclusion specific measures requested as part of a Risk Management Plan (RMP) where we would like to ensure that only identified risks shall be included. The inclusion of potential risks in this document could cause potential confusion and reduce confidence in the product.	See above change
MSD	Including in the label all theoretical risks that may be in the RMP before specific clinical data would be available is not acceptable. The label statements are usually data driven and sometimes potential concerns may not be supported by the actual data. Recommendation: The SPC should be consistent with the RMP, especially regarding Identified Risks. Potential risks noted in RMP do not automatically warrant a statement in Precautions unless there are specific measures in RMP to address those risks	See above change.
Roche	Specific measures requested as part of the RMP… this section has to be regularly reviewed and updated to ensure appropriate information. Section to be regularly reviewed and updated if needed to ensure appropriate information "Specific measures requested as part of the RMP…should be desribed in this section". Suggest to only include those measures in the SmPC that are directly relevant information for the prescriber. "Specific measures requested as part of the RMP…should be desribed in this section, if appropriate.	See above change.
AESGP	It should be emphasized that only a short description is needed.	See general principle: "The SmPC should be worded in clear and concise language."
EVM	"*In particular, specific measures requested as part of the RMP to ensure safe and effective use should be described in this* section*"* It should be clarified what is expected regarding the RMP and some examples may be helpful. More precise information, and reference to the risk	See above change.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	minimization action plan of the RMP, would be preferable. Most of the measures usually mentioned in a RMP, i.e. surveillance of identified risks, education of health professionals, or instauration of PMS study do not seem appropriate in the SmPC. Propose to modify the sentence as follows: *"In particular, specific measures requested as part of the risk minimization action plan of the RMP to ensure safe and effective use should be described in this section"*	

- Special patient groups that are at increased risk or are the only groups at risk of experiencing product or product class-related adverse reactions (usually serious or common), e.g. elderly, children, patients with renal or hepatic impairment (including the degree of impairment, e.g. mild, moderate or severe), patients having an anaesthesic or patients with cardiac failure (including in this case the NYHA Classification for example). Cross-reference to section 4.8 on the differential effects in terms of frequency and severity of the specified adverse reaction should be provided.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
Roche	*Related to second and third bullet point:* It will most likely increase the amount of information and tables to be provided in section 4.8 substantially if it is required to provide for each special patients group, which ADRs are increased at which frequency. This might not be in line with experience we have regarding HA requests to keep the info in 4.8 as concise as possible. It is mentioned to include the degree of impairment e.g. mild-moderate-severe. Alternative proposal would be to include the physiological range below or above which not to give X, to make this more clear for the prescriber.	Comment taken into account; see above change. Degree of impairment is given as an example. The SmPC guideline should be read in conjunction with the CHMP guidelines on hepatic and renal impairment.
Pharmiceut-ics LLC	There is a slight overlap between the criteria listed under bullet point 2 and 3. Change text under bullet point 3 as follows: "Circumstances where all patients are at risk of a specified adverse reaction but the frequency or severity of the reaction differs in particular sub-populations." Note that the example attached to the text of bullet point 3 illustrates the scenario described in bullet point 2. Either move example to bullet point 2 or detach from	Bullet point deleted because of the overlap.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	3.	
AESGP	The example given in Section 4.4 of the difference in headache frequency between children and adults reflects a very low threshold for inclusion in this section. It will result in an over inclusive approach and if this is not intended a better example would be preferable.	See above
Pharmasymbiosis Ltd:	You might consider changing this sentence to: 'e.g. of 20% of adults and 40% of children using a product experience headaches, then section 4.4 of the smPC should state that there is a much greater risk of of headache in children when compared to the risk in adults and cross refer....etc..	See above

- Serious adverse reactions to which the ~~prescriber~~healthcare professionals needs to be alerted, the situations in which these may occur and the action that may be required, e.g. emergency resuscitation.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
MSD - 3rd and 4th bullet	In some instances the frequency or severity of a given reaction may not be known. Recommendation: information on the different effects in terms of frequency and severity (when known) of the reaction should be provided. Frequency only would not justify elevation to precaution section (to change frequency "and" instead of "or" "and severity alone". Recommendation to provide an example of severity and frequency	See change above. The following bullet point has also been deleted because of overlap.

~~•When the outcome of an adverse reaction is particularly serious and/or frequent, this could be emphasised by presenting the statement at the top of this section.~~

- If there are particular risks associated with starting the medicinal product (e.g. first dose effects) or stopping it (e.g. rebound, withdrawal effects), these should be mentioned in this section, together with the action required for prevention.
- Any measures which can be taken to identify patients at risk and prevent the occurrence, or detect early the onset or worsening of noxious conditions. If there is a need for awareness of symptoms or signs representing early warning of a serious adverse reaction, a statement should be included.
- Any need for specific clinical or laboratory monitoring should be stated. Recommendation for monitoring should address why, when and how the monitoring should be conducted in clinical practice. If dose reduction or other posology is recommended in such circumstances or conditions, this should be included in section 4.2 and cross-referenced here.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
EFPIA	It is questionable whether some clinical practices are harmonized across EU countries. The recommendation for monitoring should address the rationale and known precautions related to abnormal findings. The sentence should be changed with the following: *Recommendation for monitoring should address why, when and how monitoring should be conducted in clinical practice, if applicable.*	"Clinical practice" should not be interpreted as detailed local or regional procedure. It is acceptable to add *"when"*. Adding "*if applicable*" is not necessary (e.g. the sentence introducing the bullet points asks that information should be included where relevant).
MSD	This bullet can be combined with the first bullet on page 11 as both related to information from the RMP. In addition, recommendations for "how" monitoring should be conducted in clinical practice may be difficult to include as this may differ from country to country. Please delete "how" or elaborate further with an example	The two bullet points address two different bases for warnings. When specific clinical or laboratory monitoring is recommended it should be described as accurately as possible.
Pharmasymbiosis Ltd	Surely, the how and why of monitoring cannot be prescriptive unless there is a compelling reason for it and must be left to the individual hospital. As such it does not seem appropriate information to be included in an SPC	It is not in the remit of the SmPC to give general advice on the treatment of particular medical conditions. On the other hand specific aspects of the treatment related to use of the medicinal product or its effects should be mentioned. Therefore, specific monitoring advice related to the concerned medicinal product should be included.

- Any warnings necessary for excipients or residues from the manufacturing process.
- For herbal preparations containing alcohol, ~~a warning~~ information ~~based on~~ about the ~~total~~ ethanol content in the medicinal product should be included in accordance with the Guideline on excipients in the label and package leaflet of medicinal products for human use.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
ESCOP	Regarding the statement on the alcohol content of herbal preparations, this should not necessarily present a "warning" e.g. in cases of a low ethanol content. The expression "information" would be more appropriate being in accordance with respective guidelines on the labelling.	Agreed. See above

- Any warnings necessary with respect to transmissible agents (e.g. Warning of Transmissible Agents in SmPCs and Package Leaflets for Plasma-Derived Medicinal Products (CPMP/BPWG/BWP/561/03).
- Subjects or patients with a specific genotype or phenotype might either not respond to the treatment or be at risk of a pronounced pharmacodynamic effect or adverse reaction. These may arise because of non-functioning enzyme alleles, alternative metabolic pathways (governed by specific alleles), or transporter deficiencies. Such situations should be clearly described if known.
- Any particular risk associated with an incorrect route of administration (e.g. necrosis risk with extravasation of intravenous formulation, or neurological consequences of intravenous use instead of intramuscular use), should be presented, with advice on management if possible.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
ESNO	Need to know consequences in case of wrong way of administration (i.e. for IV route extravasations necrosis risk, burns, or IV instead of IM with neurological consequences etc…) and reverse medications /and or actions In special population: add interaction with anaesthetics	Agreed; see above proposals
BfArM	In various Member States the Prohibited List of the World Anti-Doping Agency (WADA) will be considered in the package leaflet. There, it will be stated that the use of this medicinal product may result in positive findings during doping controls. It would be appreciated to base this warnings upon a harmonised wording already stated in the SmPC to achieve a one way processing of including such warnings into product information. In case of the active substance is listed on the Prohibited List of the World Anti-Dopjng Agency an advice should be included, that the use of the medicinal product may result in positive findings during doping controls. The Prohibited List contains substances and methods classified by categories (e.g., steroids, stimulants, gene doping).	There is no direct legal requirement for doping statements to be included in the SmPC. Section 4.4 could be suitable for adding this information; however, this would require a cross-EU recommendation to address consequences in term of consequence, workload, update and liability. Furthermore the Prohibited list of the World Anti-Doping Agency is already public.

In exceptional cases, especially important safety information may be included in bold type within a box.

Any adverse reactions described in this section or known to result from conditions mentioned here ~~must~~should also be included in section 4.8.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
AESGP	Although this is agreed, there are circumstances where adverse events are mentioned in 4.4 in the context of class effects only and without evidence of an observed effect with the product, these events	See below

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	should not be mentioned in section 4.8. It should be stated that this does not apply to events which are included in Section 4.4 only in the context of class effect.	
EFPIA	Additional clarity for handling class statements would be welcome (see proposal). Theoretical risks should not be mixed with observed risks. There may be minor structural or chemical properties in a molecule that could spare it from the class effect and this could be an important consideration for patients and prescribers. Provide additional guidance for handling class statements and the reconciliation of the information in Sections 4.4 and 4.8, i.e., guidance should state that, if a class effect is mentioned in Section 4.4, but the effect/ADR has not been observed with the specific product, then the effect/ADR should not be listed in Section 4.8 of that product's SmPC.	Section 4.8 should centralise any relevant safety information including potential class effect even if only theoretical with a new product of a class; see guidance in section 4.8. Information should appear in section 4.4 when the risk leads to a precaution for use or when healthcare professionals have to be warned on this risk.
PGEU	Insert a new paragraph with the following text *"Include the following statement: <Any adverse reaction experienced by patients and brought to the attention of the healthcare professional should be reported.>"* This is a way of encouraging reporting by healthcare professionals.	Proposal for encouraging reporting by healthcare professionals is noted. This should be further investigated after the ongoing legislative review of the EU pharmacovigilance system.
MEB	Usually the word "professionals" refers to doctors and nurses. The word 'provider' has a broader meaning and also includes laboratory assistants, etc.	Healthcare professionals may be interpreted with a broad meaning and is the term used in the regulation. See also related comment at the end of this section.
EFPIA	Deletion of the statement referring to immunologics makes this statement unclear as to what products are being referenced. The sentence is also incomplete. Proposal: *"Any special precautions to be taken by persons handling ~~such products~~ immunologicals and administering them to patients, including risks to pregnant healthcare professionals, together with any precautions to be taken by the patient, should be included in this Section, with a cross-reference to section 6.6 or 12."*	See last comments in the last paragraph of this section and the new proposed possible subsection under section 4.2 – Method of administration.

Specific interference~~action~~ with laboratory~~biological~~ tests should be mentioned when appropriate, e.g. Coombs test and Beta-lactams. They should be clearly identified with a subheading, e.g. "*Interference with serological testing*".

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
Pharmiceut-ics LLC	For reasons of clarity, replace "biological tests" by "laboratory tests".	See above
BPWP	BPWP had risen in its 2006 comments that in the core SPCs for plasma-derived medicinal products, interactions with laboratory tests have been systematically included under 4.5 Interaction with other medicinal products and other forms of interaction. BPWP consider that 4.5 is the better location for these interactions. According to the current text of the SPC guideline, Section 4.5 covers clinically relevant interactions for the medicine itself, interactions with other medicines that are important for the other medicine, interaction with herbal medicinal products, food or pharmacologically active substances not used for medical purposes. Therefore, it has always seemed logical to BPWP that interaction with laboratory tests should appear in this section. Furthermore, the laboratory interactions in the core SPCs for plasma-derived medicinal products are not relevant to the condition to be treated by the medicinal product; they are interactions with a laboratory test that would be done for other reasons. Move 'Specific interaction with biological test should be mentioned when appropriate, e.g. Coombs test and Beta-lactams.' From Section 4.4 to Section 4.5.	This issue was discussed with BPWP in the light of various examples in the field of blood products or not. Agreeing that such information shall be clearly identified within the SmPC and that it refers more to "interference" than to "interaction", the recommendation has been revised as shown above.

In general, descriptions of warnings and precautions regarding pregnancy and breast-feeding, ability to drive and use machines, and other aspects of interactions should be dealt with in sections 4.6, 4.7 and 4.5, respectively. However in specific cases of major clinical importance it might be more appropriate to describe specific precautionary measures in this section, e.g. contraception measures, or when concomitant use of another medicine is not recommended, and with cross reference to section 4.5, 4.6, or 4.7.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
MHRA, Vigilance and Risk Management of Medicines Division	In the section 'Paediatric population' it states that "when long-term safety data are necessary but not yet available it should be stated in this section". This should also be stated for *other* populations in which the drug is indicated.	Such information can be part of this section when healthcare professionals have to be warned on risk related to lack of long-term safety data. It has been underlined for paediatric population below because the need for long-term safety data may be more frequent in children (and with broader potential consequences) than in adults.
EBE	It is understood that the possibility of automatic substitution of a reference product with a biosimilar,	See answer to EBE general comment.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	or vice versa, is not addressed in the assessment of the marketing authorisation application. The EMEA's "Questions and answers on biosimilar medicines" (EMEA/74562/2006) states: "Since biosimilar and biological reference medicines are similar but not identical, the decision to treat a patient with a reference or a biosimilar medicine should be taken following the opinion of a qualified healthcare professional." It would be helpful, therefore, to include in the SmPC some advice in this respect. Add the following to section 4.4: *"In the case of biological products, where more than one product is available for the same indication (e.g. following approval of a biosimilar medicinal product), the following statement, or similar, should be included:* *"Changes from {Product Name} to other {common name} preparations should be done under strict medical supervision.""*	The need for general recommendation for therapeutic management goes beyond the scope of the SmPC.
AESGP	Description of potential contraception measures are required to be described in 4.4 and 4.6. If this is the intention, cross-references should be added. It is suggested that it might be appropriate to include a warning about concomitant drug use that is not recommended. For some highly interactive drugs this could result in duplication of much of the interactions section.	Consistent with above recommendation Appropriate use of cross-reference should be ensured in such case.

Paediatric population

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
EFPIA	Please clarify that this section can be excluded for products with no paediatric indication and only applies to warnings/precautions that are only relevant in one or more paediatric subsets (as is done in Section 4.5.) Proposal: ***Paediatric population*** *When the product is indicated in one or more subsets of the paediatric population and there are ~~W~~warnings and precaution for use that are specific to the paediatric population or any subset of the paediatric population, they.should be identified under this sub-heading ~~when the product is indicated in children~~.*	Agreed

When the product is indicated in one or more subsets of the paediatric population and there are ~~W~~warnings and precautions for use that are specific to the paediatric population or any subset of the paediatric population, they should be identified under this subheading ~~when the product is indicated in children~~. Any necessary warning or precaution in relation to long-term safety (e.g. on growth, neuro-behavioural development or sexual maturation) or specific monitoring (e.g. growth) in the paediatric

population should be described. When long-term safety data are necessary but not yet available, it should be stated in this section. Warnings should be included in case of possible significant or long-lasting impact on children's daily activities, such as learning ability or physical activities, or in case of impact on appetite or sleep pattern.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
Alcon Laboratories	It is stated that "warnings and precaution for use specific to the paediatric population or any subset of the paediatric population should be identified under this subheading when the product is indicated in children." There will be for some time SPCs which do not have specific indications for use in children, nor is the use in children contraindicated. It would be helpful to have a clarification in the guidelines to cover this situation and also regarding the provision of safety information in children under these circumstances.	See above the second bullet point (as well as recommendation for section 4.2 and 4.8) foreseeing the possibility to include information on safety in children even if the product is not indicated in children.
TEDDY	It is important to indicate if the drug can be administered to the paediatric population and even if there is the probability of interferences with lactation or other food. Briefly indicate if the drug can be administered to the paediatric population and probable interferences with lactation or other food While is fully acceptable that 'the lack of data alone must not lead to a contraindication', it seems to be necessary to underline the risk of an off-label use to Medical Doctors and Pharmacists. A similar statement should be mandatory in patients leaflets of the same drugs. Risks for using the products in lack of a paediatric indication (in all or in defined subpopulations) should also be underlined when the product is not indicated in children. When long-term safety data are necessary but not yet available, it should be stated in this section. The long-term safety data have been systematically investigated in very few drugs, thus this general statement is likely to be a "standard statement" for most drugs and may cause undue anxiety to patients and parents. The manufacturers and the regulators need to justify this statement based on the biological and pharmacological grounds.	Posology and mode of administration in paediatric population will be described in section 4.2 if the product is indicated in paediatric population. Interaction with food will be addressed in section 4.5, and 4.2 or 4.4 in case of particular recommendation. Information related to breastfeeding is described in section 4.6, and 4.3 or 4.4 in case of particular recommendation. Safety concerns in paediatric population will be described in the SmPC even if there is no indication. The recommendation regarding PL is acknowledged. Agreed; the statement is only expected when there is a known safety signal and its long-term consequences are not yet known as the long-term safety data are unavailable.
EVM	*"[…]Warnings should be included in case of possible impact on children's daily activities, such as learning ability or physical activities, or in case of impact on appetite or sleep pattern."* To limit the scope to significant and/or long-lasting impact.	Agreed. See above

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	Propose to modify the sentence as follows: *"[…]Warnings should be included in case of possible significant or long-lasting impact on children's daily activities, such as learning ability or physical activities, or in case of impact on appetite or sleep pattern."*	

If measures are requested that are specific to the paediatric population for which the product is indicated (e.g. as part of a Risk Management Plan), these measures should be described in this section.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
IPFA	Mention the specific measures requested in the Risk Management Plan on paediatric population	See above.
MEB	We propose to mention the last paragraph regarding administration directly after the paragragh about handling and administration, because both paragraghs give information about the administration of the product	Agreed; see next comment
EVM	*"Any warnings or precaution for use […] with cross-reference to 6.6".* Propose to remove the paragraph from "Paediatric population section" and to include it as a general condition in 4.4	Agreed; see next comment
Roche	This sentence is not specific for the paediatric population and is a repetition of a sentence in a former paragraph (page 12, paragraph no. 4 "Any special precautions to be taken by persons handling such products and administering them to patients, including risks to pregnant healthcare professionals, together with any precautions to be taken by the patient, with cross-reference to section 6.6 or 12"). Suggestion: delete in this place	Agreed; the above two statements have been merged and transferred to the sub-section "method of administration"] in section 4.2; *<Precaution to be taken before manipulating or administering the product>*
EFPIA	'Any warnings or precautions related to the manipulation or administration of the product by patient or carers (e.g. for a cytotoxic product) should be mentioned here with cross-reference to 6.6. 'Suggest that the last sentence of this section be moved so that it refers to the whole section and does not look like it refers only the preceding paragraph on the paediatric population.	See above

~~Any warnings or precautions related to the manipulation or administration of the product by patient or carers (e.g. for a cytotoxic product) should be mentioned here with cross-reference to 6.6.~~

4.5 Interaction with other medicinal products and other forms of interaction

This section should provide information on the potential for clinically relevant interactions based on the pharmacodynamic properties and *in vivo* pharmacokinetic studies of the medicinal product, with a particular emphasis on the interactions, which result in a recommendation regarding the use of this

medicinal product. This includes *in vivo* interaction results which are important for extrapolating an effect on a marker ('probe') substance to other medicinal products having the same pharmacokinetic property as the marker.'

Interactions affecting the use of this medicinal product should be given first, followed by those interactions resulting in clinically relevant changes on the use of others.

Interactions referred to in other sections of the SmPC should be described here and cross-referenced from other sections.

The order of presentation should be contraindicated combinations, those where concomitant use is not recommended, followed by others.

The following information should be given for each clinically relevant interaction:

a. Recommendations: these might be

- contraindications of concomitant use (cross-refer to section 4.3),
- concomitant use not recommended (cross-refer to section 4.4), and
- precautions including dose adjustment (cross-refer to sections 4.2 or 4.4, as appropriate), mentioning specific situations where these may be required.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
BfArM:	Add abullet point Interaction with oral contraceptives (cross-refer to section 4.6)	Not systematically necessary here however recommendation for cross-reference between the two sections has been added in section 4.6.

b. Any clinical manifestations and effects on plasma levels and AUC of parent compounds or active metabolites and/or on laboratory parameters.

c. Mechanism, if known. For example, interaction due to inhibition or induction of cytochrome P450 should be presented as such in this section, with a cross-reference to 5.2 where *in vitro* results on inhibition or induction potential should be summarised.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
EFPIA	List of CYP3A4 interacting drugs is becoming longer and longer. Would it be possible to have a clear recommendation on how to handle such information in the SmPC?	Particular emphasis should be made in section 4.5 on the interactions, which result in a recommendation regarding the use of this medicinal product. See also the CHMP concept paper on the need for revision of the note for guidance on the investigation of drug interactions, including the presentation of information

Interactions not studied *in vivo* but predicted from *in vitro* studies or deducible from other situations or studies should be described if they result in a change in the use of the medicinal product, cross-referring to sections 4.2 or 4.4.

This section should mention the duration of interaction when a medicinal product with clinically important interaction (e.g., enzyme inhibitor or inducer) is discontinued. Adjustment of dosing may be required as a result. The implication for the need for a washout period when using medicines consecutively should also be mentioned.

Information on other relevant interactions such as with herbal medicinal products, food, alcohol, smoking or~~,~~ pharmacologically active substances not used for medical purpose, should also be given. With regard to pharmacodynamic effects where there is a possibility of a clinically relevant potentiation or a harmful additive effect, this should be stated.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
MSD	Smoking may influence metabolism by certain CYP 450 Enzymes. Information on other relevant interactions such as with herbal medicinal products, food, alcohol, smoking or, pharmacologically active substances not used for medical purpose, should also be given. Recommendation: is not to address smoking separately but together with the above listed interactions.	Agreed; see above.

In vivo results demonstrating an absence of interaction should only be mentioned here if this is of major importance to the prescriber (e.g. in therapeutic area where potentially problematic interactions have been identified such as with anti-retroviral medicines).

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
Pharmiceut-ics LLC	Does "in vivo" here mean "in man"? Is this really meant to imply that strong evidence from *in vitro* studies that there is *no* interaction with e.g. CYP3A4 inhibitors is NEVER be a sufficient basis for a statement in this section (provided the information is considered to be important for prescribers)? Leave sentence unmodified: "~~*In vivo*~~ results demonstrating an absence of interaction should …"	In vitro results should be provided in section 5.2. (see recommendation "c" above)

If no interaction studies have been performed, this should be clearly stated.

Additional information on special populations

If there are patient groups in which the impact of an interaction is more severe, or the magnitude of an interaction is expected to be larger e.g., patients with decreased renal function (in case the parallel pathway is renal excretion), paediatric patients, elderly etc, this information should be given here.

~~It should be stated whether~~ If interactions with other medicinal products depend~~s~~ on polymorphisms of metabolising enzymes or certain genotypes, this should be stated.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
EMEA	It is proposed to clarify that such statement needs only to be made if there is any information to provide. Proposed change: *~~"It should be stated whether~~ If interactions with other medicinal products depends on polymorphisms of metabolising enzymes or certain genotypes, this should be stated."*	Agreed
Roche	This sentence does not only apply to special populations, and should be moved up to the beginning of section 4.5. Sentence to be included following first paragraph of section 4.5 and slightly amended as follows: "*It should be stated whether interactions with other medicinal products depends on polymorphisms of metabolizing enzymes or certain genotypes, if known*."	See above

Paediatric population

Information specific to a subset of the paediatric population should be given here if there is an indication for the particular age group.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
EFPIA	Advises only to include information when the product is indicated in children. If a Marketing Authorisation Holder has conducted paediatric interaction studies but a paediatric indication has not been approved for the product – this information will not be made available in the SmPC to clinicians. This is not appropriate. Proposed change: *"Information specific to a subset of the paediatric population should be given here if there is an indication for the particular age group. If relevant data on interaction studies in children exists but the product is not indicated in children, the data should be located in Section 5.1 and a reference placed here."*	If the product is not indicated in children, information could be included as part of additional information on special populations (see above).

The resulting exposure and clinical consequences of a pharmacokinetic interaction can differ between adults and children, or between older and younger children. Therefore;

- Any identified treatment recommendations should be given in relation to concomitant use in the paediatric subset(s) (e.g. dose adjustment, extra-monitoring of clinical effect marker/adverse reactions, therapeutic drug monitoring).

- , ~~i~~If the interaction studies have been performed in adults, the statement 'Interaction studies have only been performed in adults' should be included.

- If the extent of an interaction is known to be similar in a paediatric age group ~~as~~to that in adults, this should be stated.

- If this is not known, this should also be stated.~~cannot be assumed, specific treatment recommendations, including any dose adjustment, should be given for concomitant use of products in the paediatric subset (e.g. dose reduction, extra monitoring of clinical effect marker/adverse reactions, therapeutic drug monitoring)~~.

The same applies to pharmacodynamic drug interactions.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
EFPIA	"If the extent of an interaction is known to be similar in a paediatric age group as in adults, this should be stated. If this cannot be assumed, specific treatment recommendations, including any dose adjustments, should be given for concomitant use of products in the paediatric subset (e.g. dose reduction, extra monitoring of clinical effect marker/adverse reactions, therapeutic drug monitoring)" Please reword this paragraph to clarify the underlying assumption that paediatric data is available to support the wording (and to what extent).	See revised wording above
EVM	"…*If the extent of an interaction is known to be similar in a paediatric age group as in adults, this should be stated"* EVM considers that for medicines that have only a paediatric indication, there is not need to mention that studies have been performed in children and that interactions in adult population have not been assessed.	No comment

In cases of ~~an~~ food interaction ~~with food~~ leading to a recommendation on co-administration with a meal or specific food, it should be ~~noted, if possible,~~specified whether this is relevant for ~~children~~ paediatric use (especially newborns and infants) whose diet ~~may be totally~~is different (100 % milk in newborns ~~versus maybe 0 % in adults~~) ~~compared to the study setting leading to the recommendation~~.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
AESGP	The instructions given on food interaction (i.e. with milk) would be more appropriately placed in posology, as already stated there in the update. Cross refer as applicable.	Comment taken into account; see 4.2.
EFPIA	In the Paediatric population subsection the instructions given on food interaction (i.e. with milk) would be more appropriately placed in posology, as already stated there in the update. Cross reference as applicable.	Comment taken into account; see 4.2.

Overall, section 4.5 should be presented in the simplest possible way to highlight the interactions resulting in a practical recommendation regarding the use of the medicinal product. Presentation in a tabulated format may help where interactions are numerous and various, such as with anti-viral products.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
AESGP	It would seem more logical that the final paragraph starting by *"Overall…"* be at the beginning of the section.	Not necessary.

4.6 Fertility, ~~P~~pregnancy and lactation

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
MPA	Preferably the heading in section 4.6 should include fertility as well as pregnancy and breast-feeding. If it is not possible to change the heading, the fertility section should be moved to section 4.4. Revision of heading also requested by BfArM:	Agreed
EFPIA	Title of this section is not appropriate as it deals with information on contraception and fertility on top of pregnancy and breast-feeding. Change the title to "4.6 Fertility, pregnancy, and breastfeeding ~~lactation~~" Order of subparagraph should be "Fertility, Women of childbearing potential / Contraception in males and females, Pregnancy, Breast feeding) Place the paragraph "Fertility" at the beginning of section 4.6.	See above Lactation is considered suitable for the heading since it covers breastfeeding as well as other aspects such as reduction of lactation. Order could be adapted in practice when the main message is on fertility
INFARMED	Breastfeeding / breast-feeding should be written consistently through the document.	Breastfeeding will be used through the document

General ~~recommendation~~principles

Efforts should be made by the Marketing Authorisation Applicant or Holder to provide the reasons for the recommendations for use in pregnant or lactating women and in women of childbearing potential. This information is important for the healthcare professionals informing the patient.

In the overall assessment, all available knowledge should be taken into account, including clinical studies and post-marketing surveillance, pharmacological activity, results from non-clinical studies, and knowledge about compounds within the same class.

Efforts should be made to update the recommendations for use during pregnancy and lactation on the basis of increasing human experience in exposed pregnancies which eventually supersede the animal data.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
Roche	If no clinical data, strong non-clinical data could provide important information (as also mentioned on page 15 under "breastfeeding"). "Recommendation in relation to breast-feeding will be based on clinical data, when available, since they supersede non-clinical data. If no clinical data is available, conclusions from animal studies can be included".	Consistent with above general principles for this section.

~~'Contra-indication in pregnancy' should be supported by human data (teratogenicity or fetotoxicity) or by strong nonclinical data. Recommendation in relation to breast-feeding will be based on clinical data, when available, since they superseed non-clinical data.~~

In case of contra-indication, this should be included in section 4.3.

~~Efforts should be made by the Marketing Authorisation Applicant or Holder to provide the reasons supporting or not recommendations for use in pregnant or breastfeeding women, and in women of childbearing potential.~~

The following should be mentioned:

Women of childbearing potential / Contraception in males and females

Recommendations on the use of the medicinal product in women of childbearing potential should be given when appropriate including the need for pregnancy test, or contracepti~~on~~ve measures. Where an effective contraception is required for patients or partners of patients during treatment or for a defined period before starting or after ending treatment, the rationale should be included in this section ~~(see Annex 1)~~. If contraceptive measures are recommended, there should also be a cross-reference to section 4.5 (and possibly 4.4) in case of interaction with oral contraceptives.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
BfArM	Add: In case of interaction with oral contraceptives, information should be given (cross-refer also to section 4.5).	See above revised text considering that information on interactions with oral contraceptives should be described in section 4.5, and, warning would probably be justified in case of need for contraception and risk of interaction with oral contraceptive.

Pregnancy

In general, clinical and non-clinical data should be followed by recommendations.

With respect to nonclinical data,

- only conclusions of the reproductive toxicity studies should be included in this section. ~~The species in which the product has been tested can be specified if they differ from the species recommended by the guidelines.~~ Further details should be provided in section 5.3.

~~the conclusions of nonclinical reproductive toxicity studies are not necessary and should not be mentioned if a product is known to be teratogenic in humans or if it is known to be safe in humans.~~

With respect to clinical data,

- the section should include comprehensive information on relevant adverse events reported in the embryo, the ~~foetus~~fetus, neonates and pregnant women, when appropriate. The frequency of such events (for example the frequency of birth defects) ~~may~~ should be specified when available.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
EFPIA	Although a pre-existing statement, the requirement to provide frequency information in the pregnancy subsection requires knowledge of the denominator which is seldom available for spontaneous reports and there are too few pregnancies in clinical trials to provide any meaningful data. This seems to be at odds with the guidelines for the calculation of frequencies for adverse reactions. Reporting rate could be offered as an alternative, if appropriate to data available	See below
Roche	Information should be specified when available as all information is appreciated by pregnant women when making a decision as to whether to terminate a pregnancy. Data should be updated at the same time as the SmPC is updated. 'The frequency of such events (for example the frequency of birth defects) should be specified when available.'	Agreed
AESGP	Although a pre-existing statement, the requirement to provide frequency information in the pregnancy subsection requires knowledge of the denominator which is seldom available for spontaneous reports and there are too few pregnancies in clinical trials to provide any meaningful data. This seems to be at odds with the guidelines for the calculation of frequencies for adverse reactions. Reporting rate could be offered as an alternative, if appropriate to data available.	Frequency requested only when available. To be read in conjunction with the CHMP/SWP guideline on reproduction and lactation.

- the section should specify the extent of the human experience if no adverse events have been reported in pregnancy ~~(no experience, limited experience)~~.

~~Consequently, the paragraph should include~~With respect to the recommendations:

~~a)Clinical data from human experience in pregnancy with the frequency when appropriate.~~

~~b)Conclusions from developmental studies, which are relevant for the assessment of the risk, associated with exposure during pregnancy. Only malformative, fetotoxic and neonatal effects should be mentioned in this paragraph. Further details should be included in section 5.3 when appropriate.~~

~~c)~~a) Recommendations on the use of the medicinal product during the different periods of gestation, including the reason(s) for these recommendations should be given. ~~A sentence should provide the reason(s) of these recommendations.~~

~~d)~~b) Recommendations for the management of exposure during pregnancy when appropriate (including relevant specific monitoring such as foetal ultrasound, specific biological or clinical surveillance of the ~~foetus~~fetus or the neonate) should be given.

Cross-references can be included in sections 4.3, 4.4 and 4.8, as appropriate.

Examples of ~~the~~ wording ~~of~~for this section are ~~given in Annex I~~annexed to the CHMP/SWP guideline on reproduction and lactation.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
MHRA	Why has the 'o' been reinstated in 'fetus' ? 'fetus' instead of 'foetus'.	Agreed
EFPIA	Pregnancy, Initial "a)" and "b)" Data on the risk of products used (or misused) during pregnancy and lactation are very often not obtainable from clinical studies but valuable information may come from the post-marketing experience. Developmental studies are usually not the source for such information. Conclusions from ~~developmental studies~~ clinical studies and the post-marketing surveillance which are relevant for the assessment of the risk associated with exposure during pregnancy.	Taken into account: see general principle above in this section.

~~***Breastfeeding***~~***Breastfeeding***

If available, clinical data should be mentioned (exposed breastfed infants) as the conclusions of kinetic studies (plasma concentrations in breastfed infants, transfer of the active substance and/or its metabolite(s) into human milk…). Information on adverse reactions in nursing neonates should be included if available.

Conclusions from non-clinical studies on the transfer of the active substance and/or its metabolite(s) into milk should be given only if no human data are available.

~~If available, clinical data should be mentioned including the conclusions of the studies on the transfer of the active substance and/or its metabolite(s) into human milk (positive/negative excretion,~~

~~milk/serum ratio). Further details should be included in section 5.2. Information on adverse events in nursing neonates should be included if available.~~

~~The above sentence has been deleted in the SWP guideline; should not it be kept?~~

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
MHRA **Vigilance and Risk Management of Medicines Division**	Where the drug or its metabolite appear in milk, consideration should be given to estimating the size of the dose likely to be delivered to the nursing infant.	Should be considered as part of the assessment: see CHMP/SWP guideline on reproduction and lactation.

Recommendations should be given to stop or continue ~~breast-feeding~~breastfeeding and/or to stop or continue the treatment in cases where treatment or ~~breastfeeding~~breastfeeding discontinuation is recommended, and the reason should be provided.

~~Conclusions on animal studies on the transfer of the active substance and/or its metabolite(s) into milk should be given only if no human data are available.~~

Example wordings ~~to be used in~~ for this section are annexed to the CHMP/SWP guideline on reproduction and lactation.~~in Annex 3.~~

Fertility

The main information on the possible effects of the medicinal product on male and female fertility ~~must~~should be included in section ~~here~~4.6.

~~The paragraph~~This section should include:

a) Clinical data if available.

b) Relevant conclusions from nonclinical toxicity studies if available. Further details should be included in section 5.3.

c) Recommendations for the use of the medicinal product when pregnancy is planned but fertility might be affected by treatment.

~~If necessary, c~~Cross-references ~~can~~ could be included in section 4.3, ~~as~~ if appropriate.

If ~~case~~ there ~~is~~are no fertility data at all, then this should be clearly stated.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
MHRA	Correct this last added sentence "*If case there is no fertility data, this should be clearly stated.*" to: *"If there are no fertility data, then this should be clearly stated."*	Agreed; see above.
AESGP	The sentence *"If case there is no fertility data, this should be clearly stated"*. needs rewording. Should this say *'...fertility data from clinical experience…'* or *'….human fertility data…'*? Suggest rewording, and that a standard statement for this situation is provided.	See rewording above. A single standard statement may not reflect all possible situations.

4.7 Effects on ability to drive and use machines

On the basis of the pharmacodynamic and pharmacokinetic profile, reported adverse reactions and/or specific studies in a relevant target population addressing the performance related to driving and road safety or using machines, specify whether the medicinal product has a) no or negligible influence b) minor influence,~~or~~ c) moderate influence or ~~e~~d) major influence on these abilities. ~~Effects of the disease itself on these abilities should only be discussed in exceptional circumstances.~~ Other important factors that affect the ability to drive and use machines should be considered if ~~relevant~~known, e.g. duration of the impairing effect and the development of tolerance ~~of~~for adverse reactions with continued use.

For situations ~~b and~~ c and d, special warnings/precautions for use should be mentioned here (and also in section 4.4 for situation d).

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
DRUID	Especially for benzodiazepines, most frequently used psychotropic medicines, it has been documented in several pharmacoepidemiological studies that the half-life of the benzodiazepine is a relevant factor in determining the association between the use of the medicine and patients' involvement in road accidents. In describing the specification concerning the influence of the medicine most experts agree that categorization should be applied in order to give clear messages to the patient. It would be in concordance with opinions of experts and existing experience with categorization systems, and would improve communication with patients to use 4 descriptions of possible influence (no or negligible, minor, moderate, major) instead of 3. Information on effects of medicines on ability to drive should also mention factors that are relevant to describe the change of impairing effects based on e.g. the duration of the impairing effect (important for medicines such as hypnotics) and the development of tolerance to adverse impairing effects with continued use. ***Proposed revised text:*** *On the basis of (…), specify whether the medicinal product has a) no or negligible influence b) minor; c) moderate influence or d) major influence on these abilities. (…). Other important factors that affect the ability to drive and use machines should be considered if relevant, e.g. duration of the impairing effect and the development of the tolerance to adverse reactions with continued use.* *For situations b,c and d, special warnings/precautions for use should be mentioned.*	Agreed; see above. However, information on duration is difficult to know and predict at the level of individual patient. It should therefore be limited to known information. Cross-reference to section 4.4 has been aligned with recommendation on this section.
EFPIA	"For situations b and c, special warnings/precautions for use should be mentioned." Please clarify: does this mean that if the product has an influence on the ability to drive, a warning should be included in Section 4.4? Or should the warning be	Cross-reference to section 4.4 has been clarified and aligned with recommendation on this section.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	included in Section 4.7? It is proposed that the warnings/precautions be stated in Section 4.7. Categories alone might potentially be misleading. On the basis of the pharmacodynamic and pharmacokinetic profile, reported adverse reactions and/or specific studies in a relevant target population addressing the performance related to driving and road safety or using machines… It is felt problematic to extend the list of situations where an impact on the patient's reaction could be seen, as it still leaves open other equally important situations. It is proposed to find a more general approach as shown in the proposal. This would then also need to be addressed in the heading. Proposed change: *"On the basis of the pharmacodynamic and pharmacokinetic profile, reported adverse reactions and/or specific studies in a relevant target population addressing the patient's ability to concentrate and react where these ability is of particular importance, e.g. performance related to driving ~~and road safety~~ or using machines, specify whether the medicinal product has a)…"*	Proposal covers too broad a range of activities
Pharmasymbiosis Ltd	Are you able to provide examples of what might constitute exceptional circumstances?	Since it is not the remit of the SmPC to give general advice on the treatment of particular medical conditions, the sentence has been deleted.
BfArM:	The three levels of possible influence on car driving safety or performing dangerous tasks are not fully sufficient. a) no or negligible influence - no warning will be stated b) minor or moderate influence or - a standard waning may be sufficient c) major influence on these abilities. A more specified warning would be necessary in most cases to explain how to behave best d) no active participation is possible, car driving or any similar cannot be allowed. This level "d" is not explicitly mentioned so far but should clearly be separated from level "c" which allows active participation in traffic under specific circumstances and / or precautions. Add: or d) will not allow any active traffic participation.	The existing levels cover the different possible intensities of effects that medicines can have on the ability to drive. The additional proposal can be considered a recommendation due to a major influence of a product which could be translated as a special warning or precaution for use.
MEB	Information about road safety like walking on the street should not be mentioned in the SPC. Depending on the response of the individual patient, a decision should be made regarding road safety.	Ability to drive and use machines encompasses various activities such as biking which is also an important component of road

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
		safety like driving. When appropriate, it is important to provide such information for safety of patients.
AESGP	It seems unclear how these categories are assigned, and especially the consequences thereof. Either warnings/precautions need to be stated, or not. Categories might potentially be misleading.	The chosen category has to be justified on a case by case basis.
EVM	Propose to add other statements in line with QRD template Propose to modify as follows: *"On the basis of the pharmacodynamic and pharmacokinetic profile, reported adverse reactions and/or specific studies in a relevant target population addressing the performance related to driving and road safety or using machines, specify whether the medicinal product has a) no or negligible influence b) minor or moderate influence or c) major influence on these abilities d) No studies on the effects on the ability to drive and use machines have been performed and e) Not relevant"*	d) is not informative and should be deleted from the QRD template e) is self understanding and does not need to be added in the guideline.

4.8 Undesirable effects

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
EADS	Instructions should ask that tolerability and safety are not confused, as a safety issue can sometimes be inadvertently buried within a plethora of standard adverse events data. - Common problems of use and serious safety issues could be highlighted separately. - In addition to classifying the frequency of adverse events, it may be helpful to indicate the time frame when events might be expected (at least to distinguish between early onset events and those associated with long-term use).	Comments acknowledged and consistent with the guideline, however the difference between tolerability and safety may not be obvious and could cause confusion. When necessary, it could be part of the characterisation of some adverse reactions (see section 4.8 c). It is agreed to put more emphasis on the need to inform on the timing of adverse reaction (see below).
EBE	*4.8 Undesirable effects* As is already acknowledged in other EMEA guidance, biosimilars are not generic products, and there may be differences, particularly in the safety profile, between a biosimilar and its reference product. It is important, therefore, that this is reflected in the guideline on the SmPC. *a. Summary of the safety profile* 1st paragraph	See answer to EBE general comment. A biosimilar can be authorised if the application shows that the biosimilar medicine is similar and as safe and effective as the

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	If any important differences have been identified between the adverse reaction profile of a biosimilar and that of its reference product, it would be helpful to physicians to include this information in this sub-section. Amend as follows: "The summary of the safety profile should inform on the most serious and/or most frequently occurring adverse reactions. *In the case of biosimilar medicinal products, any important differences in these adverse reactions in comparison with the reference product should be mentioned.*" *b. Tabulated summary of adverse reactions 3rd paragraph* In the case of biosimilar products, the paragraph that introduces the table should clarify whether the source of the information was derived from the SmPC of the reference product or data on the biosimilar product itself. Amend as follows: "The table should be introduced by a short paragraph stating the source and the extent of the safety database (e.g. from clinical trials, post-authorisation safety studies or spontaneous reporting). *In the case of biosimilar medicinal products, safety information derived from the reference product should be differentiated from data on the biosimilar product itself.*"	biological reference medicine. Safety of the reference medicine and of the biosimilar is therefore expected to be similar. As for any other medicines, some risks may not be excluded and will be addressed in the risk management plan. The guideline foresees the possibility to inform on specific product-related risks
Roche	For section 4.8 Undesirable effects, it is recommended to provide information in the following order: a) Summary of the safety profile b) Tabulated summary of adverse reactions c) Description of selected adverse reactions d) Paediatric population e) Other special populations In some sections, special populations are mentioned before paediatric population. Suggestion: keep consistent order throughout the SmPC, i.e. always paediatric population first, then special populations No guidance is given on how to handle drugs for which no clinical data are available, i.e. the only data available relates to spontaneous data, no references to the first approved label. *Please provide guidance on what is expected for old and established drugs for which clinical data is not available, or not obtained according to current standards.* For Drugs developed in the 70ties/80ties, clinical data are available, however, the quality of the data is	Comments acknowledged. Consistency has to be balanced with the need for flexibility to highlight relevant special population information for each particular medicine in order of importance. In the case of section 4.8, there should always be a specific sub-section for the paediatric population (unless irrelevant). The principles set-out in this guideline are applicable to all medicinal products. The application of those principles for a particular medicinal product will depend on the scientific knowledge on the medicinal product, the legal basis of a marketing authorisation and public health needs.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	not according to the current standard (e.g. different dictionaries used for the coding of AEs, no validation of the data etc.) Furthermore, a huge amount of post marketing data is available which may in some cases provide even more information on the safety profile of the Drug than clinical studies do. A more pragmatic approach for section 4.8 is needed for Drugs developed before 1990. Proposal for the guideline: "For Drugs developed before 1990, a different approach for the undesirable effects section may be applied and agreed between the MAH and the competent authorities." For CP/MRP products: Involvement of EMEA/RMS Proposal for nationally authorized products: Competent authority which assesses the PSUR agrees on section 4.8 on behalf of all the EU national competent authorities. The restructuring of this section into sub sections is good idea. The summary of the safety profile is an improvement as is the recommendation to provide non serious adverse event information which occurs at the start of therapy as provided in the example.	Comment acknowledged
Pharmiceut-ics LLC	Using the term *undesirable effect* throughout the entire section (and the entire SmPC guideline) would prevent the confusion that could result from the use of the term *adverse reaction* in Volume 9a as including individual adverse events for which the reporter sees a reasonable possibly of causation. Such adverse events (in Volume 9a called *adverse reactions* or *suspected adverse reactions* [see Vol 9a Glossary]) are not (necessarily, automatically) adverse reactions for the purposes of labeling. Avoiding the term adverse reactions throughout the SmPC guideline would make clear that the standards for considering an item as an adverse reaction for reporting purposes and the standards for including an items in labeling as undesirable effect are different. Use the term *undesirable effect* throughout the entire section (and the entire SmPC guideline).	The first paragraph of the section defines which adverse reactions should be included in section 4.8 of the SmPC. This definition is consistent with Volume 9A definition of an adverse reaction.

This section should include all adverse reactions from clinical trials, post-authorisation safety studies and spontaneous reporting for which, after thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or on findings from epidemiological studies and/or on an evaluation of causality from individual case reports. Adverse events, without at least a suspected causal relationship, should not be listed in the SmPC.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
Pharmiceut-ics LLC	The current wording might be confusing for an international audience. This audience could misinterpret the current statement to imply that there could be adverse reactions (undesirable effects) for which there is NOT at least a reasonable possibility of causation by a product. Replace the term adverse reactions by a neutral term (e.g. adverse phenomena or adverse experiences). If correct, clarify (outside the SmPC guideline) that the new wording ("at least a reasonable possibility") is not intended to establish a threshold that is higher or lower than before.	Adverse events and adverse reactions are international standard terms widely used in pharmacovigilance and defined in Volume 9A. Creation of a new term would be confusing.
Roche	This might be difficult to understand as it implies including all adverse reactions reported spontaneously for which a causal relationship is a reasonable possibility. Although adverse reactions from clinical trials can be assessed based on comparative incidence this is not possible for spontaneous events not reported in trials. Also if the clinical trials show no evidence for a reaction how would one assess the potential of spontaneous reports.	This is part of the assessment of clinical safety.
BfArM	It is stated that ALL adverse reactions (with a causal relationship to study drug) should be included. However, in practice, when ADRs are numerous and therapy consists of a combination of drugs (e.g. in HIV-infection), applicants tend to set a CUTT-OFF at a certain reporting frequency (e.g. >2-5%). It is suggested to include a statement whether/ when such a proceeding is considered acceptable.	The SmPC should be specific to the product. Identification of adverse reactions related to the product is part of the assessment of clinical safety.
Alcon Laboratories	The sentence 'Adverse events without at least a suspected causal relationship, should not be listed in the SPC' has been deleted in the proposed version. Although the new text does include the statement "a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility" we think that the former sentence should still be retained for clarification.	Agreed; see above.
AESGP	We do not agree with deleting the sentence "Adverse events, without at least a suspected causal relationship should not be listed in the SPC"	Agreed; see above.

~~At the time of marketing authorisation, t~~The content of this section ~~must~~should be justified in the Clinical Overview of the marketing authorisation application based upon a best-evidence assessment of all observed adverse events and all facts relevant to the assessment of causality, severity and frequency. This section ~~must~~should be regularly reviewed and, if necessary, updated with the aim to ensure appropriate information to health care professionals on the safety profile of the product. ~~T~~In addition, the whole section could be revised at the renewal of the marketing authorisation, where the safety profile of most products is likely to be well established, and thereafter at each of the three-yearly PSUR.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
AESGP	This paragraph requires a full review of the section at renewal, and at 3-yearly renewal. This seems unnecessary, given that MAHs should be monitoring for AEs and revise as required. This section of the paragraph should be deleted.	This recommendation is consistent with the guideline on the processing of renewals in the centralised procedure which also reminds that none of the changes introduced at renewal should substitute for the marketing authorisation holder's obligation to update the marketing authorisation throughout the life of the product by variation procedure as data emerge.
EFPIA	We appreciate the clear definition that only 'adverse drug reactions' should be included in Section 4.8. It is acknowledged, that it should be a joint effort of the company and the regulator to ensure that Section 4.8 does indeed focus on ADRs. Because causality is inherent in the definition of an ADR, any statement on a causal association might seem superfluous. However, in reality we have to accept a different situation: • Some adverse drug events, considered by both the MAH and the competent authority as not having 'a reasonable possibility' of being related to the drug, have made their way into Section 4.8. This may be because these events were added as precautions in Section 4.4 or were added, for example, for historical reasons. • In practice, the robustness of the data to support causality may differ, depending on different sources. • For older products, it will be impossible to achieve that Section 4.8 complies with the defined standard. For scientists working on efficacy and safety of drugs there is a clear and important difference if there is definite proof of a causal relationship and the situation where the causal relation is a "reasonable possibility". By withholding information on the *weight of the body of evidence* important nuances in information are withheld. For a prescriber, who has to counsel the patient, it will be important to know if a particular side effect is definitely associated or if there is a reasonable possibility that it is related. Therefore, it is important to share balanced information on uncertainty that is *universal* with those most involved. For these reasons, we feel that an accurate and balanced communication of risk to prescribers (and via the prescribers also to the patients) has to take into account that there may be	Discussion on causality will be part of the assessment of each individual product. Adverse reactions can be characterised as foreseen below in section c; this could encompass the causality issue if necessary.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	differences in the degree of causality of an association. This section should include all adverse reactions from clinical trials, post-authorisation safety studies, and spontaneous reporting for which, after thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility (i.e. there are facts (evidence) or arguments to suggest a causal *relationship),* based, for example, on their comparative incidence in clinical trials, or on findings from epidemiological studies and/or on an evaluation of causality from individual case reports. 'If relevant, statements on the strength of a causal association may be included.	
EVM	"The whole section could be revised at the renewal of the marketing authorisation, where the safety profile of most products is likely to be well established, and thereafter at each of the three-yearly PSUR." It should be clarified, whether this sentence means that that safety changes to the SmPC can be modified through the renewal procedure and do not need to be assessed through a variation procedure. Refer to renewal guideline EMEA/CHMP/2990/00 rev. 3 of 20 October 2005.	This recommendation is consistent with the guideline on the processing of renewals in the centralised procedure which also reminds that none of the changes introduced at renewal should substitute for the marketing authorisation holder's obligation to update the marketing authorisation throughout the life of the product by variation procedure as data emerge.
Pharmiceut-ics LLC	This sentence can be misinterpreted to de-emphasize the need for updates of this section whenever new undesirable effect become known, either based on new clinical studies or in the framework of continuous postmarketing surveillance. Remove the entire sentence.	See above

It is important that the whole section is worded in concise and specific language and does not include information such as claims regarding the absence of specific adverse reactions, comparative frequency statements other than as described below, or statements of general good tolerability such as "well tolerated", "adverse reactions are normally rare", etc. Statements on lack of proof of causal association should not be included.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
Roche	Consider amending the final sentence to…'Statements on lack of proof of causal association should not be included unless in extraordinary circumstances and with strong justification.	Not necessary. Any deviation from this guideline should be justified in the relevant Overview or Summary in the marketing authorisation application.

In order to provide clear and readily accessible information, section 4.8 should be structured according to the following recommendations:

a. Summary of the safety profile
b. Tabulated summary of adverse reactions
c. Description of selected adverse reactions
d. <Paediatric population>
e. <Other special population(s)>

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
ESCOP	The proposed structure of this chapter (a - e) should only be used as far as sufficient information is available. In case no adverse reactions have been reported (e.g. for many herbal preparations), it does not seem useful to include headings without information.	Comment acknowledged
EFPIA	Confirmation would be appreciated that the subtitles in the guideline are not considered as required subheadings in the SmPC. As such, it is strongly recommended to refrain from allocating a, b, c etc in cross-references. Therefore, a different provision is necessary for an appropriate cross-reference. Where additional details about an adverse reaction are described in section c), the reaction concerned should be highlighted, for example with an asterisk, and~~, "see section c)"~~ a cross-reference to the place where the information is provided should be included as a footnote.	The subtitles have been used for the purpose of clarity of the guideline. For individual SmPCs, they could be used if necessary to facilitate reading or identification of information on a particular undesirable effect or on a special population.

a. ***Summary of the safety profile***

The summary of the safety profile should provide information ~~on~~ about the most serious and/or most frequently occurring adverse reactions.

If known, it may be helpful to indicate the timing when adverse reactions occur. ~~I~~For example, inn order to prevent early discontinuation of a treatment, it may ~~also~~ be important to inform about non-serious adverse reactions that are frequent in the beginning of the treatment but may disappear with its continuation. Another example would be to inform on adverse reaction associated with long-term use. Frequencies of cited adverse reactions should be stated as accurately as possible. ~~It~~ This summary of the safety profile should be consistent with the important identified risks mentioned in the Safety Specification of the Risk Management Plan. The information ~~must~~should be consistent with the Table of Adverse Reactions (see section b). Cross-reference should be made to section 4.4 if relevant risk minimisation measures have been proposed in that section.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
EFPIA	The RMP and SmPC are two different documents, with different intentions, and the RMP is not intended to be made publicly available. Moreover, not all the information presented in the RMP is relevant for the SmPC. Specific direct reference to the RMP in the SmPC must not be made. Should the approach from the draft proposal	It is not expected to make direct reference to the RMP in individual SmPCs. See above There is already a recommendation to ensure

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	nevertheless be taken, it is suggested to modify the sentence to reflect the fact that the RMP and SmPC should be kept consistent and aligned, as appropriate. It is also suggested to give this recommendation for the entire safety sections of the SmPC and therefore to move this sentence under page 4 (e.g. "principles of presenting the information: The RMP and SmPC should be kept consistent and aligned, as appropriate"). It should be noted that such recommendation might also trigger more variations.	consistency with the RMP in section 4.4 which is the other main section for which it would apply.

An example of an acceptable statement is given below:

> *'At the beginning of the ~~rapy~~treatment, epigastric pain, nausea, diarrhoea, headache or vertigo may occur; these reactions usually disappear within a few days even if treatment is continued. The most commonly reported adverse reactions ~~over the course of therapy~~during treatment are dizziness and headache, both occurring in approximately 6% of patients. Serious acute liver injury and agranulocytosis may occur rarely (less than 1 case per 1,000 ~~users~~patients)'*

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
MSD	This may oblige the MAH to include some theoretical/potential risk that may not be confirmed by the actual data Recommendation: Add "confirmed by the clinical study data" and add better definition and examples of what type of data from the RMP we need to include in the label.	The text states that the summary of safety profile should be consistent with the important identified risks, not that all identified and potential risks should be mentioned.
Roche	The guidance regarding the summary of the safety profile is nonspecific and may give rise to totally different descriptions for drugs of the same class with similar safety data owing to different interpretation by an individual MAH. In addition, it appears to be a summary of the 3 important safety sections in the SPC: Contraindications, Special Warnings and Precautions for use and Tabulated summary of Adverse Reactions. There is a risk of either having a lengthy SPC with duplication of information or a sketchy safety summary which may be mis-used by the prescribing doctor as a substitute for these 3 important safety sections. Consider either cancellation of this section or provision of a specific guidance to its writing as follows: The summary of the safety profile should list the most serious ADRs with cross reference to the warnings and precautions section and the most common ADRs with cross reference to the tabulated summary of adverse reactions.	The proposed rewording is not sufficiently detailed to ensure proper interpretation and application in a consistent manner for different products.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
Pharmiceut-ics LLC	Spell out the principles of accurate citation of frequencies that are illustrated in the example of an acceptable statement provided below the paragraph, and offer the possibility to mention background rate, where they are relevant. This sentence could be reworded as follows: *"Frequencies of cited adverse reactions should be stated as accurately as possible, providing crude incidence proportions for undesirable effects that are classified as common or very common. For undesirable effects classified as uncommon or rare, the use of these frequency terms is appropriate. Where specific rates are cited, the placebo rate or rate in an untreated group may be mentioned where the magnitude of this rate is of relevant."*	The proposed rewording is not considered necessary, as the requested information can be provided elsewhere in the section (e.g. section c).
AESGP	Summary of the safety profile: including a summary of safety profile consistent with the safety specification of RMP runs a risk of quickly becoming out of date and will also be potentially very duplicative of the proposed tabulated summary of adverse reactions. Omit this section.	Not agreed. SmPC has to be kept updated. The tabulated list of adverse reactions will be comprehensive and therefore inappropriate for presenting the summary of the safety profile.

b. ***Tabulated ~~summary~~ list of adverse reactions***

A single table (or structured listing) should list all adverse reactions with their respective frequency category. In some cases for common or very common reactions, and when it is necessary for the clarity of the information, frequency figures may be presented in the table.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
MEB	Only in exceptional cases frequency figures should be used in the table. In order to avoid that frequency figures will be mentioned too much, we proposed to change “some” into ‘exceptional’.	Possibility of presenting figures has been limited to common and very common reactions (see also comment below).
Roche	In the paediatric sub-section (d) the frequency of ‘common’ and ‘very common’ adverse events needs to be provided within bracket. It would be helpful to do the same in the adult population section	See above
EFPIA	With regard to the classification very common to very rare: there should be a provision in the guidance for rare diseases where the total patient numbers are small. Anything below 2% frequency is potentially 1 subject or less.	The same standard has to apply to all medicines including rare diseases. The guideline offers the possibility to describe the safety database or to characterise some adverse reaction.

Separate tables ~~for separate indications~~ are ~~only~~ acceptable in exceptional cases ~~circumstances, e.g. when the underlying disease influences~~ where the adverse reaction profiles markedly differ depending on the use of the product. For example, it might be the case for a product used for different indications (e.g. ~~in~~ an oncology ~~as well as in~~ and a non-oncology indications) or at different posologies.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
EFPIA	The revised guideline more firmly states that the default rule is a single table in section b. However, it is not indicated how the problem of trying to use a single table to accurately portray adverse reactions from disparate sources which can include efficacy trials, long-term controlled safety trials, post-authorisation safety trials, epidemiology studies and spontaneous reports is to be resolved. For example, frequencies of adverse reactions can be calculated from clinical trial safety data, but only reporting rates can be applied to spontaneously sourced safety data. Thus, these data should be presented separately. Furthermore, it is appreciated that in the current draft a possibility is given to deviate from the default single table. We would like to point out however, that apart from the indication, there might be other situations in which the adverse drug reactions profile is so different that presentation in separate tables would be beneficial for the prescriber. In the guidance, this is already acknowledged by allowing a separate table to be presented in sub-section 'Paediatric population'. For other special populations, gender-specific indications, dosage forms or products that are also used as add-on medication, a separate table could be more illustrative than a single table (while adding a note in another section can easily be overlooked). The decision should be data-driven by necessity. We therefore propose the following: • More explicitly allow a separate presentation within the same table (e.g. via stratification) of Adverse Drug Reactions (ADRs) obtained from studies and ADRs obtained from spontaneous reporting. • Soften the 'exceptional circumstances' allowing separate tables and expand the current example with other examples of possible exemptions. Maintain the option that in some cases (e.g. if the number of ADRs is very limited) this may be done outside a tabulated format. Proposal: *"A single table should list all adverse reactions with their respective frequency category, as appropriate, but the data in the table may be stratified to separate presentation of clinical trial data from data obtained from spontaneous reports. In some cases when it is necessary for the clarity of the information,*	Taken into account (see above revision). The purpose of the single table is to be informative to healthcare professionals by integrating comprehensive data from different sources. Use of several tables should therefore remain exceptional. The guidance on the estimation of frequency of adverse reactions will facilitate integration of data from various sources. The subsequent subtitles of sections 4.8 will allow characterisation of some adverse reactions if necessary.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	frequency figures may be presented in the table. Separate tables are acceptable in ~~exceptional~~ circumstances where ~~when the underlying disease affects~~ the adverse reaction profile is markedly different. For example, ~~it might be the case for a product used in an oncology as well as in a non-oncology indication~~ in different indications, with different dosage forms, or if the product is also used as add-on treatment, in combination with other drugs."	

The table should be introduced ~~by~~ with a short paragraph stating the source ~~and the extent~~ of the safety database (e.g. from clinical trials, post-authorisation safety studies or spontaneous reporting).

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
EFPIA	Clarification would be appreciated that 'extent' of the database does not mean statement of detailed figures, as these may become quickly outdated. Include a statement that advises against inclusion of detailed figures that are subject to change, e.g. from spontaneous sources.	Comment acknowledged; "extent" has been deleted; see above.
Roche	If some adverse reactions come from clinical trials, but others from spontaneous reporting, should they be listed in separate tables? Separate tables should be produced for data from different sources." With pooling of safety data from multiple different trials in different indications (with similar safety profile), safety information may be derived from a large total of patients (thousands). With a larger patient pool, the number of uncommon ADRs may increase substantially for some compounds (as >1 patient out of 1000 treated patients is the lower cut-off of the definition for uncommon events). This may lead to a large listing of uncommon ADRs. Specific guidance on what to do in this case would be helpful. One possibility would be to apply additional criteria, e.g. of severe and/or life-threatening (grade3/4), to the list of uncommon ADRs and only list those. This will make it more clear for a physician to which ADR attention needs to be paid (even if only reported as uncommon) and will increase the clinical meaningfulness	A single frequency should be chosen for each adverse reaction based on the analysis of the best available information. A single table is therefore sufficient and is easier to consult by healthcare professionals. Furthermore, it limits the risk of divergent information in different tables. See also section "*Further guidance on the estimation of frequency of adverse reactions*". The purpose of the tabulated summary is to list all adverse reactions and their frequency (from very common to very rare). The summary of safety profile together with section 4.3 and 4.4 will be more useful to inform on adverse reactions requiring particular attention.

The table should be presented according to the MedDRA system organ classification. The system organ class (SOC) should be presented in the order shown in ~~A~~annex ~~2~~. Adverse reactions descriptions

should be based on the most suitable representation within the MedDRA terminology. This will usually be at the Preferred Term Level (PT), although there may be instances where the use of Lowest Term Level or exceptionally group terms, such as High Level Terms may be appropriate. As a general rule, any adverse reactions should be assigned to the most relevant SOC related to the target organ. For example, PT '*Liver function test abnormal*' should be assigned to the SOC '*Hepatobiliary disorders*' rather than to the SOC '*Investigations*'. Within each system organ class, the ~~ADRs~~ adverse reactions should be ranked under headings of frequency, most frequent reactions first. Within each frequency grouping, adverse reactions should be presented in the order of decreasing seriousness. The names used to describe each of the frequency groupings should follow standard terms established in each official language using the following convention: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
AESGP	As the SPC guideline is not updated as regularly as the QRD template, the information in the Annex of the SPC guideline is not in line with the current Appendix 2 of the QRD template. We propose to refer to Appendix 2 of the QRD template to avoid outdated information in the SPC guideline. *"The table should be presented according to the MedDRA system organ classification. The system organ classes (SOC) should be presented in the order shown in ~~Annex 2~~.Appendix 2 of the QRD template"*	See comment in annex (2)
EFPIA	As the SmPC guideline is not updated as regularly as the QRD template the information in Annex of the SmPC guideline is not in line with the current Appendix 2 of the QRD template. Propose to refer to the Appendix 2 of the QRD template to avoid outdated information in the SmPC guideline. *"The table should be presented according to the MedDRA system organ classification. The system organ classes (SOC) should be presented in the order shown in ~~Annex 2~~.Appendix 2 of the QRD template"*	See comment in annex (2)
EVM	As the SmPC guideline is not updated as regularly as the QRD template, the information in Annex of the SmPC guideline is not in line with the current Appendix 2 of the QRD template. Propose to refer to the Appendix 2 of the QRD template to avoid outdated information in the SmPC guideline. Propose to modify the sentence as follows: *"The table should be presented according to the MedDRA system organ classification. The system organ classes (SOC) should be presented in the order shown in ~~Annex 2~~.Appendix 2 of the QRD template"*	See comment in annex (2)
Roche	Advice to assign terms to 'the most relevant' SOC is contradicting the advice at the very beginning of the document where it details that 'hierarchy should be followed'.	It is proposed to reword the reference to MedDRA presented in the general principles. (see general principles)
MEDDRA MSSO	Consider using the convention for MedDRA terms in text, namely; the level followed by the term in italics, without any quotation marks, e.g. SOC *Hepatobiliary disorders*	Agreed

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	Existing text: For example, 'Liver function test abnormal' should be assigned to the SOC 'Hepatobiliary disorders' rather than to the SOC 'Investigations'. Proposed text: For example, PT *Liver function test abnormal* should be assigned to SOC *Hepatobiliary disorders* rather than to the SOC *Investigations*.	
EFPIA	The wording "As a general rule... For example, 'Liver function test abnormal' should be assigned to the SOC 'Hepatobiliary disorders' rather than SOC 'Investigations'," is not consistent with the new section "Principles of presenting information" (page 4, 4th bullet). It is noted that MSSO has issued a set of general recommendations on how MedDRA-coded data should be used in biopharmaceutical product labeling (MedDRA® and Product Labeling: "Best Practices" Recommendations). We believe that the SmPC guidance should be in line with these recommendations. Provide guidance that principles of presenting information should be in line with the MSSO document "MedDRA® and Product Labelling: 'Best Practices' Recommendations" Flexibility should be allowed in the retrospective use of MedDRA terms for older clinical data, which were originally presented in another classification system. A retrospective rewording of ADR information will not provide relevant new information, which may impact on the evaluation of the benefit/risk ratio. It should be clear from the text (in Annex 2) that grouping terms in a different way could only be done on the basis of the individual data. Because of the specific structure of MedDRA, it is not possible to group terms by adding up the percentages.	The recommendation in section "Principles of presenting information" has been revised to ensure consistency. MedDRA MSSO comments on the SmPC guideline have been taken into account. "MedDRA® and Product Labelling: 'Best Practices' Recommendations" are the responsibility of its author. Recommendations made above or in annex (2) leave flexibility for using the most suitable representation within the MedDRA terminology According to ICH M4E, it is important to use standardised terms to describe events and collect synonymous terms under a single preferred term and frequencies should be presented for preferred terms and for appropriately defined groupings...
Pharmiceut-ics LLC	MedDRA HLTs are rarely suitable as meaningful superordinate concepts for risk communication; most of the time they are only suitable as subsection headings. On the other hand, the PT level contains many superordinate concepts that can be used as group terms. In keeping with the spirit of Annex 2 of the SmPC guideline, reword sentence as follows: *"This will usually be at the Preferred Term Level, although there may be instances where the use of Lowest Level Terms or High Level Terms is appropriate; in exceptional situations (e.g. when suitable group terms cannot be found in MedDRA) terms or group terms which are not (yet) in the MedDRA dictionary*	Not contradictory.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	can be used."	
AESGP	Definition of frequency terms To be more efficient and clear a table should give all definitions of frequencies at the beginning of the chapter. Rather than order by decreasing seriousness, we propose that similar adverse events be grouped together within a frequency category, or even if frequencies differ, as we consider this would be helpful to the prescriber.	Not contradictory. Comment unclear in view of the overall recommendation on presenting adverse reactions within this list.
EVM	"*…adverse reaction should be presented in order of decreasing seriousness*" EVM believes that to present the adverse events in order of decreasing seriousness is not relevant and would be subject to personal judgement. Propose to delete the sentence	Evaluation of seriousness implies scientific judgment and is part of the assessment.
EFPIA	It may be difficult to always aim for a list according to decreasing medical seriousness, as this is a subjective assessment. A sentence could be added to emphasize that seriousness should be based on a medical decision by the manufacturer. Also, an addition should be made 'if appropriate'. It is also proposed to make the respective statement 'Within each frequency grouping, adverse reactions should be presented in order of decreasing medical seriousness.' optional in the QRD templates, as it sometimes is not sensible, (e.g., if only very few adverse reactions are presented. Proposal: *"Within each frequency grouping, adverse reactions should be presented in order of decreasing seriousness, if appropriate."*	Evaluation of seriousness implies scientific judgment and is part of the assessment.

In exceptional cases, if a frequency cannot be estimated from the available data, an additional category frequency 'not known' may be used. In case the expression *"Frequency not known"* is used, the following text should be added in the list of terms explaining the frequency categories: *"not known (cannot be estimated from the available data)".* The expressions isolated/single cases/reports should not be used.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
Roche	Expressions like "isolated/single cases" can be more accurate than "very rare" or "not known", in particular if the product is widely used. Allow use of such expressions. 'In exceptional cases, if a frequency cannot be estimated…..' Given the explanation for the calculation of incidence information "not known" should no longer be required. If required, please	Stating or referring to numbers of cases reported may be misleading since they inevitably will become outdated. Whenever possible, an estimate of frequency should be provided. *(cf. Report from CIOMS*

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	provide examples/explanation of when the category should be used. "Not known" provides less information than "in isolated/single cases". "…if a frequency cannot be estimated from the available data, an additional category frequency "not known" may be used." Would delete the category frequency "not known" and mention the adverse reaction without frequency.	*Working Group III and V, Geneva 1999, 2nd edition)* It is agreed that 'not known' is not informative, it is why it should be used exceptionally as a last resort
MHRA, Vigilance and Risk Management of Medicines Division	(b) A single table of ADRs with frequencies is proposed. Although spontaneous ADRs will now usually be assigned a frequency (using the 3/X rule) if there are no suitable trials from which to assign a frequency it is proposed that the term 'not known' will be used. This term is not very helpful and perhaps should be explained as a footnote to the table.	Agreed; the following sentence has been added in the guidance: *"In case the expression "Not known" is used, the following text should be added in the list of terms explaining the frequency categories: "not known (cannot be estimated from the available data)".*
Alcon Laboratories	The guideline proposal advises that only 'in exceptional cases', if the frequency cannot be estimated from the available data the category frequency not known may be used. This frequency term is currently used to classify the majority of ADR's from spontaneous reporting, and we therefore propose that the reference, " only in exceptional cases" be removed from this section.	See above.
AESGP	We object to the use of the word *'exceptional'*; most labelling updates in post-marketing will arise from spontaneous data for which it will be very difficult to calculate frequencies. The proposed guidance on how to calculate frequencies from spontaneous data is very burdensome. It is not very practical particularly for older products, where there are often no integrated databases from clinical studies. In practice most of the events identified from spontaneous reporting will be rare or very rare even applying the proposed methodology. Therefore there seems limited value of going through a complex method to get to a predicted result. Furthermore, this activity does not benefit the public health greatly. Although the revised wording states that only in exceptional cases frequencies cannot be estimated, this is does not hold true for older products where this may be a common occurrence. The use of 'not known' can mislead prescribers and patients. Its use is a particular problem for Patient Information Leaflets. Adverse reactions in this category are often very serious, where it is very important to relay the incidence 'generally rare or very rare' to help people balance the risk to them of taking the medicine. People may assume that these events could occur frequently.	See above. See also guidance on the section "Guidance on the estimation of frequency of adverse reactions"

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	We propose to assign category 'rare' to adverse reactions identified from spontaneous data and with no evidence from clinical studies. Or 'very rare' in case of extensive use of the product in the market over a long period of time and without evidence from clinical studies.	
EFPIA	Although the revised wording states that only in exceptional cases we will be unable to estimate frequencies, this is not the case for older products where this will be a common occurrence. Furthermore, it may also occur for ADRs obtained via spontaneous reporting. The use of the term 'not known' can mislead prescribers (and patients) as it could mean anything from very common to very rare. ADRs in this category are often very serious and it is very important to relay a more precise incidence. See our proposal for 'Frequency calculation for adverse drug reactions from spontaneous reporting'	See answer to EFPIA comments on the section "Guidance on the estimation of frequency of adverse reactions"

Where additional details about an adverse reaction are described in section c), the reaction concerned should be highlighted, for example with an asterisk, and, "see section c)" should be included as a footnote.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
EFPIA	When reviewing ADRs in Section 4.8, it would be helpful to have a consistent link to additional information that may be available elsewhere, e.g., Sections 4.3, 4.4 or 4.5 or 4.8c. In the Tabulated Summary, provide an asterisk or footnote if additional information on an ADR is available elsewhere, e.g., in Sections 4.3, 4.4 or 4.5 or 4.8c.	A sensible approach in using cross-references should be ensured in order not to compromise readability.

Guidance on how to estimate the frequency of an adverse reaction is provided at the end of this chapter of the guideline.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
Cambridge Regulatory Services	What is your view on order of side effects in the SmPC and PIL, as the most of the EU countries prefer to have side effects in order of severity, but some in an organ order. Is there any possibility of further harmonisation?	The guidance proposes a harmonised approach to present the list of adverse reactions: by MedDRA SOC, then by frequency, then by severity.
Roche	It would be useful to receive more clear guidance on what to do with ADRs found from combination trials,	As for any other product, there should be a single

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	when also information on monotherapy is available. Currently the guidance only allows for one single table. In stead of a single table listing all ADRs, there should be the possibility to have two tables: one table for compound X used as a single agent across different indications (where possible); one table to list all ADRS that are found with Compound X in combination therapy across indications (where possible). This way the prescriber has the overview of ADRs only related to compound X, in addition to use in combination.	table. As proposed below, a statement should be included at the beginning of the section c to point out which particular adverse reactions are usually attributable to which active substance of the combination, where known. Detailed information on the adverse reaction of each compound may be described in their respective SmPC.
BfArM:	The word "table" may encourage to use a tabulated format instead of listing ordered according to SOCs, frequencies and seriousness. There may be some case where a tabulated format is the most appropriate, but in most cases structured listings are used in the past. Additional text is proposed as shown on the right. New fourth paragraph: *"The table can be presented as a structured listing mentioning the following recommendations or in a tabulated format depending from the complexity of the adverse reaction profile of the medicinal product."*	Comment taken into account in revising the first sentence as follows: "A single table *(or structured listing)* should list all adverse reactions with their respective frequency category."
MSD	No guidance is provided in this section for combination products. Guidance in this section regarding how to integrate the tabular summary for combination products would be welcome. Thoughts for consideration are as follows. For many combination products it cannot be determined which of the component agents is associated with a particular adverse reaction and some adverse reactions may be associated with both agents. Additionally, once the combination agent is marketed newly identified adverse reactions cannot be assigned to a single component. Lastly, for combination products all adverse reactions observed with either of the components are potential adverse reactions of the combination product. Therefore, it should not be medically necessary to distinguish the components in the adverse event listing. An integrated listing of adverse events by SOC should be provided including those adverse reactions observed with the combination and or any of the individual components Recommendation: Do not to specify in the SPC to which components the AE is associated.	The case of fixed combination products is addressed under the sub section c. An integrated list of adverse reaction should be provided including those adverse reactions observed with the combination and or any of the individual components, followed by a statement pointing out which particular adverse reactions are usually attributable to which active substance of the combination, where known.
AESGP	We think that the provision of a Tabulated summary of adverse reactions needs further consideration. How will clinical trial data and spontaneous data be distinguished and how will indication specific	There is no need to inform on the safety data source of individual adverse reactions. Should there be indication

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	findings be identified? We would welcome more advice on combination products, particularly as regards what information (by component or in combination only) to include in Section 4.8 "Undesirable Effects".	specific findings; information could be described under subsection c. See above

c. ***Description of selected adverse reactions***

This section should include information characterising specific adverse reaction which may be useful to prevent, assess or manage the occurrence of an adverse reaction in clinical practice.

This section should include information characterising individual serious and/or frequently occurring adverse reactions, or those where there have been reports of particularly severe cases. The information should provide frequency and may describe for example reversibility, time of onset, severity, duration, mechanism of the reaction (if of clinical relevance), dose relationship, relationship with duration of exposure or risk factors. Measures to be taken to avoid specific adverse reactions or actions to be taken if specific reactions occur should be mentioned under section 4.4 and cross-referenced here.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
MEDEV/ ESIP	It should be clearly stated that information must be provided on the relationship of frequency of adverse reaction and the duration of use of the medicinal product. Not only is the dose relationship important. (In accordance with the definitions and the guidelines on pharmacovigilance (Vol. 9))	Agreed. "Relationship with duration of exposure" has been added above.
AESGP	In this section frequencies should be stated. It remains unclear if frequency categories or precise frequencies are expected	Frequency category will be provided under b. This section will characterise selected adverse reactions. Precise frequencies will therefore be expected.

Information on the occurrence of withdrawal reactions may be mentioned here with cross-reference to section 4.2 in case of need for tapering off or advice on discontinuation of the product.

Mention should be made here of any differences between different dosage forms in respect of adverse reactions.

In the case of combination products, ~~a statement~~information should be included ~~at the beginning of~~in this sub-section pointing out which particular adverse reactions are usually attributable to which active substance of the combination, where known.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
MSD	As noted above it is more likely than not 'that it is not known' which component is associated with which	Such information when known is important for

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	adverse reaction. It will be difficult at the beginning of this section to describe attribution to the components for some but not all of the events. It will be more informative to place that information in the description of the event particulars if known. *In the case of combination products, a statement should be included in the discussion of the selected adverse reaction pointing out which active substance of the combination the adverse reaction is associated, where known.* Recommendation: Do not to specify in the SPC to which components the AE is associated.	clinical practice. See also below.
EFPIA	The statement requested here would require another duplication of information. Relationship of certain adverse reactions to individual components of the product can either be mentioned in the general introduction or in context with the individual term. The request should therefore, be worded more openly. Proposal: *In the case of combination products, ~~a statement~~ information should be included ~~at the beginning of this section~~ pointing out which particular adverse reactions are usually attributable to which active substance of the combination, where known. This information can be provided either here, or in the general introduction or in the tabulated list.*	This subsection allows characterisation of specific adverse reactions; including which component of a fixed combination induces an adverse reaction when known. This does not prevent the presentation of this information in the summary of safety profile when the reaction is one of the most serious and/or most frequently occurring adverse reactions of the product.

Any adverse reactions resulting directly from an interaction should be mentioned here and cross-referenced to section 4.5.

This section should also inform on adverse reactions with very low frequency or with delayed onset of symptoms which may not have been observed in relation to the product, but which are considered to be related to the same therapeutic, chemical or pharmacological class. The fact that this is a class attribution should be mentioned.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
MEB	proposal to delete section c For clarity background information should not be mentioned in the SPC. It is possible to mention this information in the (E)PAR	The purpose of this section is not to provide background information which should indeed be presented in the (E)PAR but to characterise specific adverse reactions which may be useful in clinical practice for assessing, preventing or managing the occurrence of an adverse reaction.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
Alcon Laboratories	In the current SPC guidelines this information is provided in a separate paragraph section (d). and we consider that, for sake of clarity, this guidance should still be provided in a separate headed paragraph. *"d. Pharmacological Class Effects This section should also inform on adverse reactions with very low frequency or with delayed onset of symptoms which may not have been observed in relation to the product but which are considered to be related to the same therapeutic, chemical or pharmacological class. These must include reactions described under Section 4.4. The fact that this is a class attribution should be mentioned."*	It is considered sufficient to ensure that the class attribution should be mentioned.
MHRA, Vigilance and Risk Management of Medicines Division	(c) 'Description of adverse reactions' - ADRs that are serious or frequent will now be described in more detail and it is suggested that risk factors are included as part of the description and, if necessary, expressed also in section 4.4. There is a need for guidance on whether an ADR identified spontaneously should have a frequency categorisation if cases were also observed in trials (but the latter did not meet the threshold for inclusion in the CT section). E.g. If 1 convulsion was observed in the CT programme (but not added in the SPC section due to investigator causality or 1 in 10,000 occurrence) and then 10 cases are observed spontaneously and a decision is made to include in SPC - should frequency be 'not known' or 1/10,000? We prefer the latter approach. A general comment on this Section is that the best way to communicate risk to health care professionals and patients is being considered under various European initiatives e.g. proposals for a risk management guideline, consultation on pharmacovigilance legislation and activities related to improving patient information. There may be an opportunity in the future to cross-refer in the SPC guideline to other available guidance	Comment consistent with the approach of the present revision.
Roche	There are some "class effects" which are not seen with members of the same class eg statins some of which are enzyme inhibitors others which are not or very weak. So some form of qualifying statement should be allowed in relationship to the mention of class effects. Example "this particular adverse reaction is not reported despite exposure in 1 million patients."	Conclusions of pharmacoepidemiological safety studies could be mentioned in section 5.1 if it is relevant to inform prescribers on absence of a particular adverse reaction.
EFPIA	The second last paragraph of this section refers to AEs, "…with very low frequency … which are considered to be related to the same therapeutic, chemical or pharmacological class". This requirement could be deleted from this section of 4.8 and clarity improved if class effects are mentioned in section 4.4 (as suggested above). Proposal: *Delete from Section 4.8c (page 17): "~~This section~~*	Duplication of information in the SmPC should be avoided. Section 4.8 should provide comprehensive information on adverse reaction including class related

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	~~*should also inform on adverse reactions with very low frequency or with delayed onset of symptoms which may not have been observed in relation to the product, but which are considered to be related to the same therapeutic, chemical or pharmacological class. The fact that this is a class attribution should be mentioned.*~~*"* ***Add to Section 4.4*** *, a new bullet either after the present second bullet (page 11) or after the last bullet (page 112): "Adverse reactions with very low frequency or with delayed onset of symptoms which may not have been observed in relation to the product or for which causality has not been established, but which are considered to be associated with other products in the same therapeutic, chemical or pharmacological class. The class attribution should be mentioned. Likewise, if unproven reactions are included, then wording should indicate that causality has not been demonstrated."*	information. Information should also appear in section 4.4 when the risk leads to a precaution for use or when healthcare professionals have to be warned on this risk. *(See also answer to related comment in section 4.4)*

Any adverse reaction specific to excipients or residues from the manufacturing process should be included.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
AESGP	Is it required to describe frequency by formulation?	No, unless there is a significant difference that is clinically relevant

d. **<*Paediatric population*>**

A paediatric sub-section should always be included (unless irrelevant).

The extent and age characteristics of the safety database in children should be described (e.g. from clinical trials or pharmacovigilance data). Uncertainties due to limited experience should be stated.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
EFPIA	Please reword. The statement that there are limited or no data available in a certain field would suffice to convey a clear message to the prescriber. Proposal: ~~*Uncertainties due to limited experience should be stated.*~~ *If there is limited or no experience in a certain area, this should be stated*	The meaning of the sentence is to focus on the uncertainties.

If the observed safety profile is similar in children and adults this could be stated: e.g. "Frequency, type and severity of adverse reactions in children are <expected> to be the same as in adults".

Similarly, it is appropriate to state whether the safety profiles in the different paediatric subsets are similar or not.

Any clinically relevant differences (i.e. in nature, frequency, seriousness or reversibility of adverse reactions) between the safety profiles in adult and ~~in the~~ paediatric populations, or in any relevant age groups, should be described~~,~~ and ~~stratified~~ presented by age group. If there is a need for specific monitoring, this should be highlighted ~~with~~ by cross-referencing~~e~~ to section 4.4. For clinically relevant differences, a separate table listing such adverse reactions by frequency can be added and ~~stratified~~ presented by relevant age groups if appropriate. If some paediatric adverse reactions are considered common (~~≥1% and <10%~~≥1/100 to <1/10), or very common (~~≥10%~~≥1/10) the frequencies~~y need to~~ should be provided in parentheses~~within brackets~~. In case of major difference with the safety profile in adults, a summary of the safety profile in children could be presented to facilitate the presentation of the information. Available information, from any source and scientifically validated, on long-term safety in children (e.g. on growth, mental development and sexual maturation) should also be summarised, whether positive or negative, with cross-reference to section 5.1 if appropriate. Any risk factors such as duration of treatment or period at risk should be specified.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
Pharmasy-mbiosis Ltd	using 'any' source is risky particularly if the source happens to be a publication of dubious repute.	It has been made clear that information provided will be scientifically validated as a result of a scientific assessment.
AESGP	Paediatric population – A further table is suggested for the Paediatric population subsection. Amongst other changes, this will make the EU SmPC very long and could dilute the key messages	Recommendations aim to describe only clinically relevant differences between the safety profiles in adults and children.
EFPIA	'For clinically relevant differences, a separate table listing such adverse reactions by frequency can be added...' Please clarify. Should these ADRs be included in the overall table in section a as well? Or should they only be presented separately under d? When discussing frequencies in the paediatric subpopulation, it should be taken into consideration that usually, frequency statements are made prospectively and that the population may be rather small. In both cases, absolute frequencies may not be meaningful and should not be requested. Furthermore, clarification would be appreciated what 'information from any source' could refer to. Does this include consumer reports, for example, that are not confirmed by a health care professional? With respect to the request for summary of positive or negative information, it should be considered that this is the adverse reactions section and that positive information may rather belong elsewhere (e.g. section 5.1).	Section "a" asks for a summary of safety profile and not an overall table. Should the paediatric safety differences are of major clinical importance, they may indeed be highlighted in the overall summary. The same standard has to apply to all population including paediatric population. The guideline offers the possibility to describe the safety database or to characterise some adverse reaction, which may allow underlining any specificity related to the size of the population. Clarification has been added with regard to the source of information. The possibility of cross-reference to section 5.1 has been added.

If relevant, symptoms of neonatal withdrawal should be listed in a separate paragraph with cross reference with 4.6.

e. <Other special populations>

This section may include information on any clinically relevant differences (i.e. in nature, frequency, seriousness or reversibility of adverse reactions, or need for monitoring) specifically observed in other special populations such as elderly, patients with renal impairment, patients with hepatic impairment, ~~or~~ patients with other diseases or a specific genotype. Cross-reference to other sections such as 4.3, 4.4 or 4.5 may be added as appropriate.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
Roche	Include elderly and patients with other diseases with cross-reference to sections 4.3, 4.4, 4.5. Cross-reference to sections 4.3, 4.4, 4.5	Comment taken into account; see above.
EFPIA	As proposed for the sub-section paediatric, complementary guidances would be useful regarding "Other special population". Proposal: *"Information about special populations should be provided in the event of clinically relevant differences or when a specific monitoring is needed (cross-reference with section 4.4). Cross-reference to other subsections e.g. table b) could be suggested to avoid duplicate information."*	Comment taken into account; see above.
AESGP	The requirement to include special populations in the 'Other Populations' subsection will repeat information already covered previously in sections b) and c).	It is agreed that repetition should be avoided. Section c aims to characterise specific adverse reaction(s). This subsection will present differences of the safety profile of the product in a special population, if necessary.

Adverse reactions may also be related to ~~polymorphically~~ genetically determined product metabolism. Subjects or patients deficient in the specific enzyme may experience a ~~higher~~ different rate or severity of adverse reactions. This should be mentioned and where relevant correlated with data from clinical trials.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
Roche	There may be adverse reactions for specific genotypes also for other aspects, not only drug metabolism. "This section my include information specifically observed in other special populations such as elderly…..patients with other diseases or a specific genotype. Adverse reactions may also by related to	Agreed

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	polymorphically determined product metabolism."	
EFPIA	Current text is not completely correct since: Subjects or patients deficient in the specific enzyme may experience a higher or lower rate or severity of adverse reactions. Rates should not be applied to individual patients, but rather populations. The word "polymorphically" should be replaced with the word "genetically" *"Adverse reactions may be related to ~~polymorphically~~ genetically determined product metabolism. Subjects or patients deficient in the specific enzyme may experience a ~~higher~~ different rate or severity of adverse reactions."*	Agreed

Further guidance on the estimation of frequency of adverse reactions

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
EFPIA	We welcome the scientific approach given to this section. However, the current proposal contains a number of simplifications that limit the possibilities for the prescriber to interpret the information. • Frequency categories are by definition arbitrary and ADRs that are in reality close to one another but also close to the borderline between categories may fall into separate categories, making a distinction that is not medically meaningful; • It is of interest to the prescriber to know what the probability is to experience an ADR as compared to not using the medication. The revised guideline allows for the mentioning of placebo incidence rates but not in direct association with the table. Furthermore, the alternative is not always placebo/no treatment but a standard treatment. Although crude proportions seem simple, they do not give the prescriber all information that is available and needed to assess the adverse drug reaction; • Crude incidences may be misleading in cases with high background noise, even if a footnote is provided; • Crude incidences are a 'crude' estimate of reality, e.g., they do not address the issue of differing treatment periods nor other issues inherent to clinical trial design. In general, it is our opinion that prescribers should be given all information that is necessary to assess a certain ADR and is available to the company. We would also like to point out that prescribers are quite	Frequency is the standard. Addition of another expression of the risk (e.g. the relative risk) is possible within the characterisation of a particular adverse reaction and will have to be considered on a case by case basis as part of the assessment of safety data.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	used to interpreting and working with the way data are presented in, e.g., professional magazines. It is recognised that in cases where safety of drugs is an issue (e.g., in hormone replacement therapy or suicidality risk associated with SSRIs) it does make a difference whether a person is 1.5, 2 or 4 times as likely to experience the ADR and these type of approaches take centre stage. The approaches may differ, depending on the product and therefore flexibility on approach is needed. Our proposal is to allow the MAH to present for each adverse drug reaction a Relative Risk (RR) estimation alongside the crude incidence rates when these data are available and have added value. Depending on the product, the RR estimate could be calculated against placebo or other comparator. To streamline such calculations, we would be happy to discuss with regulatory authorities a consensus approach to be reflected in the SmPC guidance. Trial selection should be based on trial quality, blinding and size of the database. The calculations should also include estimates of the confidence intervals.	

The estimation of the frequency of an adverse reaction depends on the data source (i.e. clinical trial, post-authorisation safety study or spontaneous reporting), the quality of data collection and causality evaluation. If the choice of the frequency category is based on different sources, the category representing the highest frequency should be chosen unless a more specific method has been applied and thus resulted in an estimate of clearly higher validity, e.g. a pooled analysis across suitable studies.

Sources of data should use population exposed to the doses and treatment duration as recommended in the SmPC.

Reactions that are reported under different terms but represent the same phenomenon (e.g., sedation, somnolence, drowsiness) should ordinarily be grouped together as a single adverse reaction to avoid diluting or obscuring the true effect. Similarly, reactions that represent a syndrome complex should ordinarily be grouped together under an appropriate heading to avoid obscuring the full range of respective symptoms.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
BfArM	A number of adverse reactions will be part of a syndrome, e.g. allergic reactions, which should be recognised as a whole. Add the text: *"Reaction that represent a syndrome complex should ordinarily be grouped together under an appropriate heading to avoid obscuring the full range of respective symptoms. E.g. allergoid/allergic reactions – a syndrome complex with symptoms usually scattered over some system organ classes – all respective symptoms should be grouped together under the SOC "Immunologic Disorders" with the respective subheading "Allergoid" or "Allergic*	Comment acknowledged; guidance has been extended to cover the concept of syndrome (see above).

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	Reactions" thus maintaining the interrelation of these adverse reactions. Further explanations – if required – should be placed after the table."	
Roche	By grouping different terms that are representing the same phenomenon we might create some major problem for Drug Safety Reporting, because as of todays Drug Safety rules we have to report to Global Drug Safety database using exactly the same term used by the Physician who reports in to Roche. If a term used by the Reporter is "hidden" in a common term for several similar AEs, this particular AE is not listed in the SmPC and therefore will be regarded as unexpected. To take the example from this document "sedation" is suggested not be listed for a product albeit this AE would be very common. When the Reporter then uses the term "sedation" and this term is not explicitly mentioned in our SmPC this will be classified as unexpected.	According to ICH M4E, it is important to use standardised terms to describe events and collect synonymous terms under a single preferred term and frequencies should be presented for preferred terms and for appropriately defined groupings. These principles for assessing adverse events should apply for informing on adverse reaction.
EFPIA	With respect to grouping of terms, is the intent that a single term be listed as the medical concept classified in the MedDRA hierarchy and that the other subsumed terms are also retained in parentheses - which might be useful for determining expectedness and/or the need to update the table over time, e.g., "somnolence (including sedation, drowsiness)?" Should inclusion of all Lowest Level Terms listed under a given Preferred Term in the published hierarchy be considered included or subsumed terms? Please clarify how this should be done. Such percentages cannot be obtained from a straightforward analysis of the database. Simply adding up the percentages is also not correct. i.e. sedation is 0.3%, somnolence is 0.3% and drowsiness is 0.4%; then if combined these would fall into common category, but if named separately this would appear that each of them has a higher occurrence (i.e. 1%) than it really is. It would require SMQ like analytical groupings suitable for an SmPC text. If this is to be done consistently, more guidance should be given. In this context, please refer to MSSO guidance on the labelling as a reference document Provide clarification of the expectation for presentation of included or subsumed terms vis-à-vis use in expectedness determinations. Comment: Guidance on pooling of safety data of different pharmaceutical forms has been deleted. It might be appropriate to keep such guidance.	See above comment. The application of these principles is part of the assessment. Pooling of safety data of different pharmaceutical forms is not excluded as long as it does not introduce a bias (see first sentence in the section below).
Pharmiceut-ics LLC	This subsection of the guideline uses slightly inconsistent terminology for the type of rate to be used as the basis for allocating undesirable effects to frequency categories. Consider using *crude incidence proportion*. - Clarify the meaning of : "… estimation … depends	Based on comments received, only a few clarifications appeared necessary.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	on … causality evaluation."	

Adverse reactions from clinical trials

Safety data from several studies should be pooled to increase the precision of adverse reaction rates as appropriate without introducing bias (e.g. major difference in population characteristics or exposure to the product).

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
EVM	Although the process suggested in these guidelines is interesting in theory, its application to the whole life cycle of product may prove unrealistic. This approach requires that pooled analysis of safety is available, which is only possible for a short time period after the product Marketing Authorisation. After several years on the market, if new studies have been performed, a new pool will be necessary. This process is resource-intensive and cannot be performed for each new adverse event to be added in the SmPC, based on spontaneous reporting, particularly for non-serious adverse event. A lot of difficulties may be encountered for pooled analysis: difference in MedDRA versioning, absence of coding for unsolicited events in old studies, change of clinical database, change in the process of collecting the events, change in the manufacturing process, and other technical obstacles to statistical approach of integrated analysis of adverse events. New Adverse Events are created in MedDRAa every year. Therefore, these events cannot be searched before their creation. As a consequence, all Adverse Events detected by spontaneous reporting surveillance will be described in the "not known" frequency section. This will not be an exceptional situation. Propose to modify the sentence as follows: *"Safety data from several studies should be pooled to increase the precision of adverse reaction rates as appropriate without introducing bias (e.g. major difference in population characteristics or exposure to the product) if technically feasible."*	Tools are available to ensure use of MedDRA data from different versions of MedDRA

The frequency of adverse reactions should be derived from pooled placebo-controlled studies if these data are available and the databases are sufficiently large to be informative. If these data are unavailable or not sufficiently informative, active-controlled data or possibly single-arm or add-on trials databases could be used to estimate frequencies.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
Pharmiceut-ics LLC	The first sentence of this paragraph seems to imply that excess rate over placebo may be of importance for choosing the frequency category. The second sentence is obviously not compatible with such an assumption. However, the reason for making the statement that active-controlled data or possibly single-arm or add-on trials databases could be used to estimate frequencies remain unclear. Given the proposed method for estimating frequencies, both statements appear to have no obvious practical application. Clarify the intent of these statements or delete both sentences.	No clarification needed

Frequency should represent crude incidence rates (and not differences or relative risks calculated against placebo or other comparator).

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
Roche	Crude incidence rates may not be helpful if they are similar to placebo. It would be preferable to be able to show all the data necessary for a physician to make a decision.	This case has been addressed in the following sentence.

When a common, ~~or~~ very common or serious adverse reaction (e.g. suicide) also occurs in the placebo group with a relevant frequency, both incidence rates can be stated to put the risk into perspective (e.g. in subsection c).

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
ESC	The complex issue of "adverse reactions" occurring in both placebo and treated patients – which is the rule – does not seem to be solved by reporting the incidence rates of "common or very common" adverse reactions ". Less common or uncommon events may be even more alarming (i.e. suicide) and awareness of incidence rates in both placebo and treated groups may be relevant.	Agreed; see above proposed revised wording.

Adverse reactions from ~~post-authorisation~~ safety studies

The choice of the frequency category to which any adverse reaction will be assigned is based on the point estimate of the crude incidence rate derived from a study designed in such a way that specific adverse events occurring in patients within a defined observation period would have been detected and reasonably attributed to the medicinal product. In this situation, it is possible to calculate a point estimate of the crude incidence rate using standard statistical methods. In cases where the original information is expressed as an incidence density (denominator expressed as person-time), an appropriate transformation into an incidence proportion should be performed for choosing the frequency category. Normally, incidence proportions for the most representative exposure period (e.g.

1 week, 3 months, 1 year) should be used to derive the frequency category. However, this may not be appropriate if the hazard function increases over time; in this case, the adverse reaction and its frequency pattern, when clinically relevant, should be properly described in section c).

The frequency category to be chosen for each adverse reaction should not be based on differences calculated against a comparator. However, when data ~~come~~ are derived from a study with a non-exposed group and the rate difference attributed to the medicinal product is smaller than the baseline or background incidence rate, and if the adverse reaction is considered important, the background incidence may be provided (e.g. in section c).

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
Roche	The paragraphs are complex and difficult to understand with long sentences and qualifying statements, presumably written by a statistician. Also these demands are not accompanied by reasons. These demands should at least be recognisably reasonable. 'Frequency category' Again, this is a very complex sentence. Also there needs to be a rationale for this decision. Why should not differences be calculated against a comparator?	The sentences use standard terminology understandable by physicians with a basic knowledge of epidemiology or statistics. Use of a less precise terminology would dilute the message and allows variability in the text of the SmPC.
MSD	The definition of PASS studies includes clinical trials and it could cause confusion if there are two separate sections to record AEs from Clinical Trials and PASS. Please merge these two sub-sections and rename the heading: " Adverse reactions from clinical trials and post-authorisation safety studies"	See revised heading.
AESGP	The intention of the 'Adverse reactions from post-authorisation safety studies' subsection under 'Further guidance on the estimation of frequency of adverse reactions' is unclear. Clarification of the intention is needed.	The intention of this section is mentioned in the last sentence of section b) of the guidance

Adverse reactions from spontaneous reporting

The number of spontaneous reports should not be stated because the number can quickly become outdated. Frequencies based on reporting rates from a spontaneous reporting system should not be used ~~for choosing a frequency category~~to assign frequency category. In case of an unexpected adverse reaction detected from spontaneous reporting, each adequately designed study where this adverse reaction could have been detected should be reviewed to choose a frequency category. If the adverse reaction ~~had not been observed in any study~~has never been observed in clinical trials, then the upper limit of the 95% confidence interval is not higher than 3/X, with X representing the total sample size summed up across all relevant clinical trials and studies (e.g. those with a follow-up long enough to detect the adverse reaction). For example, if ~~the~~ a particular adverse reaction has not been observed among 3600 subjects exposed to the product in clinical trials and studies, then the upper limit of the 95% confidence interval for the point estimate is 1/1200 or less and the frequency category should be "rare", based on ~~a~~ worst value of the point estimate. The rationale for the frequency category for that particular reaction could be explained in sub-section c).

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
BfArM	In case of new drugs, where the clinical trial database consists of company sponsored trials only, which is also known to the regulators, the procedure for calculating frequencies of ADRs from spontaneous reporting might be appropriate. For OLDER DRUGS, however, the regulators' assessment of the validity of the database (used as denumerator for the frequency calculation), gathered by the MAH, e.g. by collating and analysing publications, may be markedly hampered by the quality of the published information. The following additional sentence is proposed as a new third sentence: *"…used for choosing a frequency category. For older drugs, the choice of a frequency category may be markedly hampered by the quality of the available information. In case of an unexpected adverse reaction…"*	This difficulty is acknowledged however the proposed sentence does not add any guidance.
MEB	to replace paragraph by: *"The number of spontaneous reports should not be stated because the number can quickly become outdated. Frequencies based on reporting rates from a spontaneous reporting system should be mentioned in the frequency category 'unknown'"* It is very difficult to calculate a frequency.	Divergent comments received on the use of "unknown". "Unknown" is not informative and could lead to misinterpretation. Whenever possible, an estimate of frequency should be provided.
Roche	AES from spontaneous reporting. Reference to epidemiological data shall be included if possible in order to better characterize and differentiate the AEs reported form the use of the product or because is an age-related event, for example The way to estimate a frequency for an adverse reaction from spontaneous reporting could lead to overestimation of the frequency. E.g. for a product that has been on the market for a long time with a huge number of patients exposed during the post-marketing phase, an estimation of a frequency comparing to clinical trials only would not necessarily represent the "real picture". Would it in such cases not be more appropriate to mention the adverse reactions without an estimate of frequency?	This section focuses on guidance for estimating frequency. When data are available, any adverse reaction can be better characterized (e.g. in informing on risk factor) for example in section c. Whenever possible, an estimate of frequency should be provided based on the available evidence. Frequencies should not be assessed on the basis of reporting rates but on data available from clinical trials or epidemiological studies.
MSD	The MAH agrees that the number of spontaneous reports should not be stated because the number can quickly become outdated. Frequencies based on reporting rates from a spontaneous reporting system should not be used for choosing a frequency category. As noted in the suggested text neither the number of reports nor the estimated exposure are reliable enough to be informative to prescribers. Utilizing the approach outlined in the proposed	Stating or referring to numbers of cases reported may be misleading since they inevitably will become outdated. Whenever possible, an estimate of frequency should be provided. *(cf. Report from CIOMS*

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	guidance still does not reliably estimate the frequency of these adverse reactions as it is dependent on the size of the clinical database which in many instances will be too small for a reliable estimate. Routine overestimation of the frequency of adverse reactions would occur and not provide meaningful information for the prescriber to interpret. The MAH proposes that the frequency of adverse reactions based on spontaneous reports is unknown. *In case of an unexpected adverse reaction detected from spontaneous reporting is detected then the frequency category unknown should be used. The number of spontaneous reports should not be stated because the number can quickly become outdated. Frequencies based on reporting rates from a spontaneous reporting system should not be used for choosing a frequency category since numbers of spontaneous reports may not reflect true incidence and tablet distribution data provides only rough estimates of exposure the frequency cannot be estimate reliably to provide useful information to the prescriber.* Recommendation: Delete text as above. Not acceptable.	*Working Group III and V, Geneva 1999, 2nd edition)*
AESGP	Adverse reactions from spontaneous reporting: This paragraph describes a method of calculating frequency categories for side effects established on the basis of evidence from spontaneous reporting for which no ADRs exist in the clinical trial database. Comment 1: in case of small clinical trial databases satisfying quality criteria the conservative approach proposed may lead to a significant overestimation and by consequence inappropriate perception of the frequency of respective side effects. For instance, a side effect that by its nature and/or the amount of cumulative post-marketing experience can reasonably be expected to be rare or very rare and which was detected by very few striking cases and for which the size of the pooled clinical trial database is less than 3,000 patients would have to be categorised as 'uncommon' or higher. This may result in non-compliance of patients. Comment 2: the situation where evidence does originate from clinical trials but only through the incidence of unrelated adverse events relative to placebo and which is not reflected by ADRs is not covered in this proposal We recommend not to change the current procedures and to use the frequency category 'not known*'. Add qualifier '* no ADRs observed in a clinical trial database of … patients'. We recommend addressing this situation. Moreover, we recommend the same procedure as outlined above.	This section only concerns estimation of frequency of adverse reactions. See above

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
Pharmiceut-ics LLC	When a common or very common adverse reaction also occurs in the placebo group with a relevant frequency, both incidence rates can be stated to put the risk into perspective (e.g. in subsection c). Adverse reactions from post-authorisation safety studies … The frequency category to be chosen for each adverse reaction should not be based on differences calculated against a comparator. However, when data come from a study with a non-exposed group and the rate difference attributed to the medicinal product is smaller than the baseline or background incidence rate, and if the adverse reaction is considered important, the background incidence may be provided (e.g. in section c). The criteria that permit the citation of specific rates for both drug and placebo/untreated group differ. Suggestion: Delete the "mechanical" criterion ("rate difference attributed to the medicinal product is smaller than the baseline or background incidence rate") for both scenarios use the criterion "relevant". In addition, we suggest that the principle approach to informing about the frequency of undesirable effects with relevant background rate be revised. For undesirable effects with relevant background rate, the current approach consists of two steps: 1. Assigning the effect to a false high frequency category 2. Compensate for the false high classification by providing rates for drug and placebo/untreated group. We suggest that in such situations the frequency category is chosen based on the rate difference, and that also the actual rates for both drug and placebo/background are provided. This approach would also generate a frequency category that can be used as is in patient information.	Proposed recommendations are unclear. General recommendation is sufficient to allow implementation on a case by case basis depending on available data and scientific evaluation.
	That decision to deviate from the general (and appropriate) rule of basing categories on crude incidence proportions with drug and to allow for a background-rate correction should be made on a case by case basis - taking into account whether the observed rate difference is relevant (but not schematically twice or more the placebo rate) AND "sufficiently real" (no overlap of, for example, 80% confidence intervals). Comment on the phrase highlighted in yellow: This could be misunderstood to mean that unimportant undesirable effects do not need to be included in the SmPC. Delete this phrase. The current draft mentions the existence of the rule of	The recommendation is implied in the example provided. The rule of 3 uses the available evidence from clinical trials and epidemiological studies. A cautionary note is not considered necessary.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	three, but does not actually recommend its use. Change wording to: " If the adverse reaction had not been observed in any study, then the following approach should be considered before deciding to use the frequency category "not known" … If the upper …". We also suggest adding a cautionary note against uncritical use of the rule of 3. Using the rule of 3 based on to small a number of exposed patients can lead to incorrect frequency categorization. Every number of exposed patients of ≤3000 will make every effect at least "rare", and every number of ≤300 will make every effect at least "uncommon", although the effect might rightly be assumed to be "very rare".	
EFPIA	The present proposal is a good attempt to replace the assignment of reporting rates based on sales or other denominator data (which are not easy to reliably estimate). We further agree that ADRs from spontaneous reports (reflecting the 'real-world' patient population) are an important addition to frequency data calculated from clinical trials. However, the present advice is to use the upper limit of a Pearson Clopper confidence interval as an estimate. This is unreasonable in itself and inconsistent with the remainder of the approach presented earlier. The 3/n rule is a simple and accurate rule for providing an upper limit of a confidence interval – it is however not a formula that provides an estimate of an incidence. The approach for the other adverse events, however, does provide estimates of incidences. Applying this rule leads to an inconsistent situation which can best be illustrated with an example. Suppose we have approximately 2500 exposed patients. If we have no cases in our clinical trials and one post marketing report and we apply the 3/2500 rule it would be allocated to frequency category 'rare'. If we have the same post-marketing report and one single case in the pooled dataset of clinical trials the frequency estimate would be 1/2500 and frequency allocation would be 'very rare'. So by having no cases we have a higher frequency than if we have 1 or even 2 cases. Apart from the described inconsistency, the above method has other disadvantages: • It is not applicable for older products or in other situations in which the extent of the relevant integrated clinical database cannot be obtained (an example is a situation when the original submission's safety data are owned by a 2nd or 3rd business entity.	The proposed 3/X rule may not be optimal but provides the best data driven estimate of the upper limit of the frequency confidence interval. The comparison of the two frequencies calculated is not relevant because the use of the 3/X rule will probably not be considered in the second case since frequency will have already be estimated through a proper pooled database where cases have been reported. It is acknowledged that there is no solution that fits all situations. It is why the guideline proposes different methods which will have to be applied as part of the assessment. Whenever possible, an estimate of frequency should be provided to Patients and Healthcare Professionals. When feasible, there is no reason to disregard a method which could help to make more accurate estimation even between "rare" and "very rare".

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	• The method is time-consuming as it implies a re-calculation of the frequency and as a consequence a revision of this section of the SmPC each time data of new clinical studies are available. In conclusion, the presentation of ADRs from spontaneous reporting is an important but a very complex issue, and there is not likely to be one solution that fits every product. Our industry proposal is based on the practical consideration that most ADRs identified from spontaneous reporting and not reported in clinical trials will be 'rare' or 'very rare' even applying the proposed methodology. Therefore, there seems limited value in going through a complex method to get a predictable result. We, therefore, propose to initially assign the category 'rare' to adverse reactions identified from spontaneous data and not reported in clinical studies. If extensive use of the product in the market over a long period of time is indicative of a different frequency, the frequency category could change to a more appropriate one. Important in this context would be the overall weight of the evidence. We would be happy to discuss other approaches with the authors of the guidance in order to come to a best feasible presentation of these data	

4.9 Overdose

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
MHRA	Management of overdose will include appropriate monitoring; however it may be appropriate to specify that monitoring requirements (e.g. ECG, or blood pressure) should be stated. Would it be possible to emphasise that guidance on management of overdose should always be evidence based and to refer to internationally accepted guidelines on the treatment of overdoses within the SPC guideline? Quite often, we find that SPCs are out of line with such guidance.	Comment taken into account; see below revised wordings.

Describe acute symptoms and signs and potential sequelae of different dose levels of the medicinal product based on all available information including accidental intake, mistakes and suicide attempts by patients.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
Pharmasy-mbiosis Ltd:	replace intake by ingestion	Not agreed. Intake broader than ingestion.

Taking into account all relevant evidence, ~~D~~describe management of overdose in man, e.g. in relation to monitoring or use of specific agonists/antagonists, antidotes or methods to increase elimination of the medicinal product such as dialysis. However, there should not be any dosage recommendation of other medicinal products (e.g. antidotes) as it could create conflict with the SmPCs of those other products. If applicable, counteractive measures based on genetic factors should be described.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
AESGP	Reference to an antidote should be limited to situations where this is available.	Consistent with recommendations.
EFPIA	"If applicable, counteractive measures based on genetic factors should be described." This needs to be clarified or an example provided. To our knowledge there are no examples of a genetic factor that could be counteractive regarding overdose. Potentially they are referring to an overdose due to metabolic deficiency based on genotype, which could be put here, e.g. dosing recommendation to avoid overdose. However, that type of information would normally be found in 4.2.	In certain circumstances, specific counteractive measures may be necessary based on the genetic make up of the subjects. Where available such information should be included.
MHRA	It is inappropriate to include advice here on the dosage of other medicinal products (e.g. antidotes) as there is the potential for this advice to conflict with the SmPCs of those other products. Dosage advice for antidotes should be discouraged in this section of the guidance.	Agreed; clarification added

Additional information on special populations

Information specifically observed in ~~other~~ special populations such as elderly, patients with renal impairment, patients with hepatic impairment, other concomitant diseases etc.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
EFPIA	It is presumed that 'other' means 'other than paediatric'. This should be specified. Proposal: *"Information specifically observed in ~~other~~ special populations (other than paediatric) such as elderly, patients with renal impairment, patients with hepatic impairment, other concomitant diseases etc."*	Comment taken into account; see above.

Paediatric population

If there are specific paediatric considerations, there should be a sub-section entitled 'paediatric ~~patients~~population'.

~~It is useful to include a special mention for those medicinal products which can cause a fatal poisoning in the special risk group of young children when just a single tablet or dose unit is ingested. This is a limited special group of medicines, which should be kept with extra care.~~Special mention should be made of those medicinal products/strength or formulation for which ingestion of only one tablet or dose unit by children can cause fatal poisoning.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
MEB	Replace “to be kept” with “to be stored” “Store” is a better word in this situation	See comment below
Pharmasy-mbiosis Ltd	This paragraph is not clear. It is not celar to understand whether the author is asking for the mention of the medicine in the SPC or mention of the extra care required for storage or both? With regards to storage, ALL. medicines are required to be kept out of the reach of children and as such, the text about extra care may not necessarily be appropriate. Suggested text is provided below> *Special mention must be made of those medicinal products for which ingestion of only one tablet or dose unit can cause fatal poisoning.*	See above proposed rewording
MHRA, Vigilance and Risk Management of Medicines Division	For all medicines (whether or not indicated for children), it would be helpful, where possible, to show the dose that causes significant acute toxicity in terms of mg/kg - this can help to predict the likelihood of serious effects whatever the size of the child	Information already requested (see first sentence of this section). See above proposed clarification for paediatric wording.
EFPIA	Clarification needed: this provision only applies to a number of very critical products, which would best be specified by the authorities. Guidance would be necessary on how to identify critical dose levels and terminology “young children…” is too vague. Furthermore, it is proposed to reconsider where such information would best be placed.	See above proposed rewording

5. PHARMACOLOGICAL PROPERTIES

Sections 5.1 – 5.3 should normally mention information, which is relevant to the prescriber *and to other health-care professionals,* taking into account the approved therapeutic indication(s) and the potential adverse drug reactions. Statements should be brief and precise~~, in particular section 5.1 should not be longer than one page~~.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
EFPIA	A new requirement has been included, that "section 5.1 should not be longer than one page". We are not in agreement with this provision for the following reasons: - With the exception of section 4.1 Therapeutic indications (which must be concise), this is the only section where an MAH can communicate to the prescribers the benefits of a product: most of the rest of the SmPC concerns risks. Arbitrary restriction of	The SmPC should not include promotional claims but should provide objective information to be the basis of information for healthcare professionals on how to use the medicinal product safely and effectively. As highlighted by the CONSORT Statement,

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	section 5.1 creates an unhelpful imbalance in the communication of benefit/risk. - Article 87 of DIRECTIVE 2001/83/EC states that: "All parts of the advertising of a medicinal product must comply with the particulars listed in the summary of product characteristics." Therefore it is critical that the relevant information is provided in Section 5.1 of the SmPC to support the information in promotional material. Explicit confirmation of benefits in the SmPC is increasingly sought by reimbursement authorities and bodies reviewing promotional materials. - The guideline demands full disclosure of paediatric efficacy results, but seeks to restrict efficacy information from use in adults. These requirements, coupled with an arbitrary restriction on the length of section 5.1, will create an unacceptable imbalance in the information provided for different patient populations, and will exacerbate the concerns expressed in the preceding two points. - The restriction on length would be particularly problematic for products with multiple indications, for vaccines (information on different schedules, different age groups, different serotypes, and other factors e.g. immunosuppression need to be included in Section 5.1) Delete: ", in particular section 5.1 should not be longer than one page." Guidance that the section should be short and concise is sufficient.	reporting of a randomized controlled trial requires a complete transparency enabling readers to understand a trial's design, conduct, analysis and interpretation, and to assess the validity of its results. The SmPC is not suitable for presenting such information in detail contrary to a public assessment report. Considering that the limit of one page is arbitrary, it is agreed to delete this provision. However, it is expected that the application of the recommendations for this section will lead to a section shorter than one page in most cases.
MSD	We are concerned with the statement that the information should be limited to one page. If numerous clinical investigations have been carried out, this is important information for the prescriber and should clearly and completely be reflected in section 5. A limitation of pages is not helpful to ensure adequate communicate of the benefits of a specific medicine. Please delete the sentence.	See above
Roche	It is mentioned that "..in particular section 5.1 should not be longer than one page." This will not be sufficient to cover all relevant clinical trial information! It needs to be clarified that this can be one page per indication e.g.	See above
AEFI	Although statements should be brief and concise, limit to one page section 5.1 is a problem. Some medicines have a big number of studies that make impossible to briefly describe them in only one page. Remove the mention that in particular section 5.1	See above

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	should be no longer than one page.	
EVM h	as a major concern with regard to section 5.1' Pharmacodynamic properties': the revised SmPC guideline establishes that "*Statements should be brief and precise in particular section 5.1 should not be longer than one page*." EVM considers that the limitation to one page is not realistic in the case of vaccines: information on different schedules, different age groups, different serotypes, and other factors, such as immunosuppression need to be included in Section 5.1. In addition, the new requirement to add a subsection on "paediatric population" will make the section 5.1 even longer. The revised SPC guideline states that "*Statements should be brief and precise in particular section 5.1 should not be longer than one page*." EVM considers that the limitation to one page is unrealistic for vaccines: information on different schedules, different age groups, different serotypes, and other factors, e.g. immunosuppression need to be included in Section 5.1 . In addition, the new requirement to add a subsection on "paediatric population" will make the section 5.1 even longer. In addition, EVM would like to draw the attention to Article 87 of DIRECTIVE 2001/83/EC states that: "All parts of the advertising of a medicinal product must comply with the particulars listed in the summary of product characteristics." Therefore, it is critical that the relevant information provided in Section 5.1 of the SPC supports the information in promotional material. Consequently, EVM considers that the limitation to one page is unrealistic in the case of vaccines. Propose to modify the sentence as follows: *"Statements should be brief and precise in particular in section 5.1 ~~should not be longer than one page~~."*	See above
AESGP	"*Statements should be brief and precise in particular section 5.1 should not be longer than one page*." This could be difficult for products with different indications. Also given that this section now also requires that the results of all clinically relevant pharmacodynamic or efficacy studies conducted in children be presented, with the results stratified by age subsets, it is not sure that a one page limit can be achieved in practice. Moreover with the new requirement to add a subsection "paediatric population" the information will always be longer than 1 page. Article 87 of Directive 2001/83/EC states that: *"All parts of the advertising of a medicinal product must*	See above

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	comply with the particulars listed in the summary of product characteristics." Therefore it is critical that the relevant information is provided in Section 5.1 of the SPC to support the information in promotional material.	
Pharmiceut-ics LLC	In particular with the addition of a requirement to also include (more) pediatric information in 5.1, this requirement will probably be rarely met. Suggestion: Delete requirement or present as a general goal (e.g. "concise")	See above

The sections should be updated regularly when new information becomes available, especially in relation to the paediatric population.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
EFPIA	The sentence "The sections should be updated regularly when new information becomes available, especially in relation to the paediatric population". This should be placed in section "Principles of presenting information" on page 4 as it is applicable for the entire SmPC.	It is correct that this statement is relevant for all SmPCs but it is presented here to make emphasis on these sections. This should not be a substitute for the marketing authorisation holder's obligation to update the marketing authorisation throughout the life of the product by variation procedure as data emerge.
EBE	The guideline states that "Sections 5.1 – 5.3 should normally mention information, which is relevant to the prescriber *and to other health-care professionals,* taking into account the approved therapeutic indication(s) and the potential adverse drug reactions." Given the potential for differences between a biosimilar product and its reference product, these sections should be transparent about the basis for approval of the product, to allow healthcare professionals and patients to make informed decisions, without prejudice, about their choice of medicinal product. Add the following : *"In the case of biosimilar medicinal products, the SmPC should contain a clear indication that the medicine is a biosimilar and the exact identity of the reference product. For example:* *"{Product Name} is a biosimilar medicinal product. The marketing authorisation for {Product X} has been approved following demonstration of similarity to its reference product {Reference Product Name}"."*	See answer to EBE general comment. The SmPC is the basis of information for healthcare professionals on how to use the medicinal product safely and effectively. Full transparent information on the basis for approval of biological products is provided in the EPAR. To further ensure transparency, it is proposed to include at the beginning of section 5.1 of SmPC of biosimilar, a statement informing that the product is a biosimilar with a reference to the EPAR. See proposal below.

5.1 Pharmacodynamic properties

Describe:

- Pharmacotherapeutic group and ATC code:

  Inclusion of the therapeutic subgroup (2nd level of WHO classification) with the 3rd (pharmacological subgroup) or 4th (chemical subgroup) level is recommended.

  If an ATC code is not yet available, this should be mentioned as 'not yet assigned'.

In case of medicinal product authorised as similar biological medicinal product, the following statement will be included:

<<(Invented) Name> is a biosimilar medicinal product. Detailed information is available on the European Medicines Agency website; www.emea.europa.eu>

- Mechanism of action (if known)
- Pharmacodynamic effects.
- Clinical efficacy and safety

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
EVM	"*Clinical efficacy and safety*" Safety data are not relevant for this section (Section 5.1). Propose to modify the sentence as follows: *"Clinical efficacy ~~and safety"~~*	Not agreed. Pharmacodynamic properties encompasses both efficacy and safety data.
ESC	This section is necessary. Reporting "Clinical efficacy and safety" under the "Pharmacodynamic properties" (5.1) is probably conventional but it does not sound as immediately clear to the clinician (which generally intends the pharmacodynamics as the biological effects of a drug rather than their clinical results). Why not to give to the "clinical efficacy and safety" the explicit dignity of a chapter?	The structure of the SmPC is legally defined. This comment could be considered in a broader discussion on regulatory information on medicine.

It may be appropriate to provide limited information, relevant to the prescriber, such as the main results (statistically compelling and clinically relevant) regarding pre-specified ~~primary~~ end points or clinical outcomes in the major trials, and giving the main characteristics of the patient population. Such information on clinical trials should be concise, clear, relevant and balanced, and should summarise evidence from relevant studies supporting the indication. The magnitude of effects should be described using absolute figures. (Relative risks or odd ratio should not be presented without absolute figures).

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
AstraZeneca	We have a significant concern with regard to the proposed change in section 5.1 of the SmPC to only include reference to pre-specified primary end points or clinical outcomes in the major trials. This restriction would make it impossible to include information around secondary endpoints which are of potential significant value for the prescriber. In the drug evaluation process, the first step to demonstrate efficacy and safety of a given medicinal product uses	Comments taken into account by deleting the restriction to primary endpoints. However, results described in this section should be relevant to the prescriber, statistically compelling and clinically relevant.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	established, efficacy endpoints which usually concern the core symptoms/signs of the condition, and, in general, will support the indication claim. The second step to show effect on e.g. in the case of Diabetes, weight loss or to provide insight in the interpretation of the effect on the primary endpoint in terms of consequences for the daily life and social functioning. With a restriction to only include primary end points in section 5.1 this valuable information would be potentially lost. There are also guidelines which cover information not directly linked to the approved indication is considered as being of value for the scientific community (section 2.3 of the Lipid disorder guideline).	
Roche	Information in section 5.1 on study endpoints is now limited to the primary endpoint. Information on secondary endpoints however can be relevant, meaningful and useful information to the prescriber and should be allowed in section 5.1. Suggest to delete "primary", i.e. for MAH to justify the medical relevance and usefulness of including information on endpoints (primary and secondary) in 5.1. It is now specified that only information related to pre-specified primary end-points may be included. In e.g. oncology setting it is important to also be able to list the secondary endpoints as they provide confirmation of the primary one which will be relevant info for the prescriber (e.g. Overall Survival as 2nd in case PFS is primary endpoint The magnitude of the effect in the trial is subject to error and therefore standard errors and confidence intervals are far more useful for the reader to make a decision about the true difference in treatments. Relative risks and odds ratios are standard ways of defining efficacy which readers are used to. Why are they not allowed?	See above Only statistically compelling information should be included. Relative risks and odds ratios are not forbidden but it is well known that they may overestimate an effect in some cases. Therefore, they should be presented with absolute figures in order to always present the real value of the effect.
EFPIA	The already limited information permitted on clinical trial results is to be further limited to "primary" endpoints or clinical outcomes. For many products, secondary endpoints may be clinically relevant and their presentation in the SmPC may be useful for prescribers. If Statistical Analysis Plan and sample size are adequate, the inclusion of such data should be permitted for the adult as well as the paediatric population. Proposal: *"It may be appropriate to provide limited information, relevant to the prescriber, such as the main results (statistically compelling and clinically relevant) regarding pre-specified ~~primary~~ end points or clinical outcomes in the major trials, and giving the main characteristics of the patient population."*	See above.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	"For confirmatory studies, ...and the results regarding pre-specified ~~primary~~ endpoints should be provided…"	
ESC	Comparative information should be included in the SmPC, in particular if this is a part of the authorization process. It should not be promotional. If the new drug has significant effects over drugs of the same class a small sentence can be allowed.	The current recommendation is compatible with this comment; it allows presentation of results of statistically compelling and clinically relevant endpoint(s) of a pivotal trial versus an active comparator.

In the exceptional cases ~~where~~ when clinically relevant information from subgroup or post-hoc analyses~~, which is considered clinically relevant,~~ is presented, it should be identified as such~~,~~ in a balanced ~~way~~manner~~,~~ ~~which~~ reflect~~s~~ings the limited robustness of both positive and negative secondary observations.

Any relevant pharmacogenetic information from ~~the~~ clinical studies may be mentioned here. This should include any data showing a difference in benefit or risk depending on a particular genotype or phenotype.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
EADS	Where active comparator trials have been undertaken (common design in diabetes studies) it may be appropriate to provide balanced cross-referencing to related medicines involved in such trials.	See above.
EBE	The SmPCs for several recently approved biosimilars include summaries of clinical data in section 5.1 that are essentially direct copies from the equivalent section of the reference products SmPC. This includes data from studies that were undertaken with the respective reference products, but does not indicate which studies were undertaken with the biosimilars. The practise of using the SmPC of the reference product has been accepted for small molecule generics, where there are no clinically significant differences in safety and efficacy between the generic and reference product. For biosimilars, however, it is recognised that there may be clinically significant differences in the safety and efficacy profile between a biosimilar and its reference product. Indeed, the CHMP 'overarching' guideline on biosimilars states that 'similar biological medicinal products are not generic medicinal products, since it could be expected that there may be subtle differences between similar biological medicinal products from different manufacturers or compared with reference products, which may not be fully apparent until greater experience in their use has	See answers to EBE general comment and EBE comment on section 5. Full transparent information on the comparability exercise is available in the EPAR. Information regarding extrapolation to an indication or not is included in the EPAR.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	been established.' Nevertheless, it does seem that the small molecule generic precedent has been applied to the SmPCs of several recently approved biosimilars since the section 5.1 of these are copies of those of the reference products. The biosimilar SmPCs therefore summarise the safety and efficacy data of the reference product, but not the safety and efficacy data of the biosimilars themselves. Inclusion of the actual safety and efficacy studies performed with the biosimilar itself would make such information clearer to the prescribing physician and patients. Therefore, information on clinical trials included in the SmPC of a biosimilar product should clearly identify those trials that involved use of the biosimilar product, and those that were conducted with the reference product or other similar products. In case the reference product has more than one indication, a statement should be included defining in which indications safety and efficacy have been demonstrated independently in controlled clinical studies using the biosimilar medicinal product and which indications have been extrapolated. Add the following to the end of the first paragraph below the bulleted list: *"Where information on clinical trials is included for a biosimilar medicinal product, it should be made clear which trials involved use of the biosimilar, and which were conducted with the reference product or other similar products. A summary of the safety and efficacy studies undertaken with the biosimilar should be included. In case the reference product has more than one indication, a statement should be included defining in which indications safety and efficacy have been demonstrated independently in controlled clinical studies using the biosimilar medicinal product and which indications have been extrapolated."*	
MSD	Obtaining sufficient specimens for genotyping in children, while theoretically important, is unlikely to be practical. The difficulty surrounding recruitment of children for clinical trials is much greater than for adults, even without asking parents for permission for genotyping. Recommendation: These recommendations should be systematically vetted with EU national IRBs. It would be very difficult to get such studies approved and enrolled. Adequate sample descriptions seem reasonable	The statement on genotyping is general and does not necessarily apply to children unless relevant.

Paediatric population

The results of all ~~clinically relevant~~ pharmacodynamic (clinically relevant) or efficacy studies conducted in children should be presented under this sub-heading.

Information should be updated when new relevant information becomes available.

Results should be ~~stratified~~presented by age or relevant subsets.

~~Where there is data but no paediatric indication~~When there are data available, but there is no authorised paediatric indication, data should be presented and a cross-reference should always be made to section 4.2, and~~4.4 or 4.3~~ as appropriate to 4.3.

In presenting results of studies, particular attention should be given to include the relevant safety data.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
Roche	Not appropriate to cross-refer to section 4.2 Posology and method of administration if the compound is not licensed for use in paediatric indication (off-label).	The cross-reference is proposed to prevent inadvertent off-label use since section 4.2 will inform if the product is contra-indicated, should not be used, or, its safety/efficacy has not been established yet in children.
EFPIA	It is stated *that 'where there is data but no paediatric indication,* a cross reference should be made to section 4.2, 4.4 or 4.3' however this is not consistent with the statement in section 4.4 where it is stated that 'warnings and precautions should be identified under this subheading *when the product is indicated for children'*. The statement should be amended to also refer to 4.8, if appropriate: The inconsistency should be clarified. Proposal: *"Where there is data but no paediatric indication, a cross-reference should be made to section 4.2, 4.3, 4.4 or 4.8 as appropriate."*	The recommendation in section 4.4 only deals with the presentation of information under a subheading or not. Wording has been revised to put more emphasis on the cross-reference to section 4.2 or 4.3. See also comment above.

For exploratory studies, the results of the main endpoints should be given with the main characteristics of the population studied and the doses used. ~~However, explanatory studies should only be described in case of lack of confirmatory studies.~~

When they are available, information and results of confirmatory studies should usually supersede and replace those of exploratory studies. For confirmatory studies, the objectives, the study duration, the doses used (and the formulation used if different from the marketed one), the main characteristics of the patient population studied (including age and numbers of patient), and the main results regarding pre-specified ~~primary~~ endpoints should be provided, whether positive or negative. ~~Other clinical outcomes may only be presented if statistically compelling and clinically relevant.~~ If data are considered inconclusive, this should be stated.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
AESGP	We propose including the fact that 'secondary endpoints should be provided as well, where relevant'. *"For confirmatory studies, the objectives, the study duration, the doses used (and the formulation used if different from the marketed one), the main characteristics of the patient population studied (including age and numbers of patient), and the results regarding pre-specified primary and, where relevant, secondary endpoints should be provided, whether positive or negative."*	See revised text above.
EVM	Propose to include that secondary endpoints should be provided as well, where relevant. Propose to modify the paragraph as follows: *"For confirmatory studies, the objectives, the study duration, the doses used (and the formulation used if different from the marketed one), the main characteristics of the patient population studied (including age and numbers of patient), and the results regarding pre-specified primary and, where relevant, secondary endpoints should be provided, whether positive or negative."*	See above
EFPIA	Propose to include that secondary endpoints should be provided as well, where relevant. For confirmatory studies, the objectives, the study duration, the doses used (and the formulation used if different from the marketed one), the main characteristics of the patient population studied (including age and numbers of patient), and the results regarding pre-specified primary and, where relevant, secondary endpoints should be provided, whether positive or negative. The inclusion of efficacy data on paediatric population should not lead to off label use. As a consequence, the mention of the doses should be used with caution. We propose to specify the dose only in case of positive results. *"For exploratory studies, the results of the main endpoints should be given with the main characteristics of the population studied~~, and the doses used~~. However, explanatory studies should only be described in case of lack of confirmatory studies.* *For confirmatory studies, the objectives, the study duration, the main characteristics of the patient population studied (including age and numbers of patient), and the results regarding pre-specified primary endpoints should be provided, whether positive or negative. The doses used should be stated only if findings are positive. Other clinical outcomes may only be presented if statistically compelling and clinically relevant. If data are considered inconclusive, this should be stated."*	See above Doses used are essential for informing on any study whether positive or negative. Information without doses would be meaningless.

The objective and the main results or the conclusion of any specific clinical safety study should also be given.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
EVM	Safety data are not relevant for this section (Section 5.1). Delete sentence.	Not agreed. Pharmacodynamic properties encompasses both efficacy and safety data
EFPIA	Safety data are usually not relevant for the section 5.1 unless a study was designed to evaluate an important safety endpoint. Such study should only be mentioned if it provides useful information that prescribers consider to be important in making appropriate clinical decisions.	Pharmacodynamic properties encompass both efficacy and safety data.
MHRA, Vigilance and Risk Management of Medicines Division	It is proposed to include a clear statement regarding studies completed in compliance with the Paediatric Investigation Plan ('PIP'). The statements of compliance recommended in the draft Commission guidance on PIPs could be included in section 5.1 of the SPC under the sub-heading 'Paediatric population.'	The purpose of the SmPC is to provide scientific information to healthcare professionals. The compliance statement should be part of the marketing authorisation.

[If the EMEA has waived or deferred a paediatric development, the information should be given as follows:]

-For waivers applying to all subsets:

"The European Medicines Agency has waived the obligation to submit the results of studies with <name of the product> in all subsets of the paediatric population in <condition as per PIP decision, in the granted indication>. See 4.2 for information on paediatric use."

- For deferrals applying to at least one subset:

"The European Medicines Agency has deferred the obligation to submit the results of studies with <name of the product> in one or more subsets of the paediatric population in <condition, as per PIP decision in the granted indication>. See 4.2 for information on paediatric use.

[For products approved under 'conditional approval' in the centralised procedure, include the following statement:]

<This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency (EMEA) will review new information on the product every year and this SmPC will be updated as necessary.>

[For products approved under 'exceptional circumstances', include the following statement:]

<This medicinal product has been authorised under 'Exceptional Circumstances'. This means that <due to the rarity of the disease> <for scientific reasons> <for ethical reasons> it has not been possible to obtain complete information on this medicinal product. The {name of Agency} will review any new information which may become available every year and this SmPC will be updated as necessary.>

5.2 Pharmacokinetic properties

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
ESC	Important, but should not be too detailed in what is not clinically applicable.	Comment acknowledged. It may be appropriate to further structure this section with this aim when developing recommendations on SmPC in view of its use in electronic tools.

Pharmacokinetic properties of the active substance(s) relevant for the advised dose, strength and the pharmaceutical formulation marketed should be given in this section. If these are not available, results obtained with other administration routes, other pharmaceutical forms or doses can be given as alternative.

Basic primary pharmacokinetic parameters, for instance bioavailability, clearance and half-life, should be given as mean values with a measure of variability.

Pharmacokinetics items, which could be included in this section when relevant, are given below.

a. General introduction, information about whether the medicinal product is a pro-drug or whether there are active metabolites, chirality, solubility, information on the population in which general pharmacokinetic data were obtained, etc.

b. General characteristics of the active substance(s) after administration of the medicinal product formulation to be marketed.

- **Absorption:** complete or incomplete absorption; absolute and/or relative bioavailability; first pass effect; Tmax; the influence of food; in case of locally applied medicinal product the systemic bioavailability; involvement of transport proteins. If available, information on the site of absorption in the gastro-intestinal tract should be stated (as it may be important for administration by enteral feeding tubes).

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
EACPT	Absorption: It should be stated, whether the substance is substrate of any efflux transporter e.g. P-glycoprotein. This information is important to judge any interaction on this level. Example: Substance is substrate of the intestinal efflux transporter P- glycoprotein. Inducers such as rifampicin may reduce bioavailability, inhibitors such as verapamil may elevate bioavailability	Agreed. The possibility to inform on involvement of transport proteins has been added for absorption as well as for distribution and elimination.

- **Distribution:** plasma protein binding; apparent volume of distribution per kilogram body weight (l/kg); tissue and/or plasma concentrations; pronounced multi-compartment behaviour; involvement of transport proteins.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
EACPT	Replace "volume of distribution" by "apparent volume of distribution per kilogram body weight (l/kg) ..."	Agreed.

- **Biotransformation:** degree of metabolism; which metabolites; activity of metabolites and contribution to effect and toxicity; enzymes involved in metabolism; site of metabolism; results from in vitro interaction studies that indicate whether the new compound can induce/inhibit metabolic enzymes.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
MPA	The following paragraph should be revised and "Contribution (if any) of metabolite(s) to the effect." further down in section 5.2 should be deleted. * **Biotransformation:** degree of metabolism; which metabolites; activity of metabolites *and contribution to effect and toxicity*; enzymes involved in metabolism; site of metabolism; results from in vitro interaction studies that indicate whether the new compound can induce/inhibit metabolic enzymes.	Agreed

- **Elimination:** elimination half-lives, ~~the~~ total clearance; inter and/or intra-subject variability in total clearance; excretion routes of the unchanged substance and the metabolites including the relative portion of the hepatic and renal eliminated fraction, involvement of transport proteins.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
BfArM	To support better dose recommendations in case of renal or hepatic impairment the relative portion of the renal and hepatic elimination should be stated explicitly	Agreed; see above

- **Linearity/non-linearity:** linearity/non-linearity of the pharmacokinetics of the ~~new compound~~active substance with respect to dose and/or time; if the pharmacokinetics are nonlinear with respect to dose and/or time, the underlying reason for the non-linearity should be presented.

Additional relevant information should be included here.

c. Characteristics in specific groups of subjects or patients

- Variations with respect to factors such as age, weight, gender, smoking status, polymorphic metabolism and concomitant pathological situations such as renal failure, hepatic disease, including degree of impairment. If the influence on pharmacokinetics is considered to be clinically relevant, it should be described here in quantitative terms (cross-referr~~al~~ence to section 4.2 when applicable).

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
CS QRD	suggestion to better describe the content of the subsection.	Agreed

d. Pharmacokinetic/pharmacodynamic relationship(s)

- Relationship between dose/concentration/pharmacokinetic parameter and effect (either true endpoint, validated surrogate endpoint or a side effect).

~~•Contribution (if any) of metabolite(s) to the effect.~~

- The population studied should be described.

Paediatric population

Results of pharmacokinetic studies in the different paediatric age groups should be summarised, with a comparison to adults if available. If appropriate, the dose producing similar product exposure as in adults could be given. The pharmaceutical form(s) used for pharmacokinetic studies in children should be stated. ~~Any u~~Uncertainties ~~because of~~ due to limited experience should be stated.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
EFPIA	The last sentence is unclear: "Any uncertainties because of limited experience should be stated". What 'uncertainties' might be covered and what examples of text to address these would suffice? Either delete this sentence or provide a re-write to make intention clear and consider the use of examples, if appropriate.	Sentence harmonised with similar recommendation in section 4.8.

5.3 Preclinical safety data

Information should be given on any findings in the ~~pre~~non-clinical testing which could be of relevance for the prescriber, in recognising the safety profile of the medicinal product used for the authorised indication(s), and which is not already included in other relevant sections of the SmPC.

If the results of the ~~pre~~non-clinical studies do not add to the information needed by the prescriber, then the results (either positive or negative) need not be repeated in the SmPC.

The findings of the non-clinical testing should be described in brief with qualitative statements as outlined in the following example ~~statement~~s:

- Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development.
- Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.
- Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows.

Findings of non-clinical studies relevant for use in the paediatric population, including juvenile animals and peri- or post- natal studies, should be presented with a discussion of their clinical relevance, under a sub-heading if necessary.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
MHRA	Inconsistent use of the terms 'preclinical' and 'non-clinical' in the section heading, in the second paragraph and in the bullet points. Use a consistent term – 'non-clinical'.	Use of 'non-clinical' is now used consistently in the text but "Preclinical safety data" has been kept in the section heading according to the legislation.

<Environmental Risk Assessment (ERA)>

Where relevant, ~~C~~conclusions on the environmental risk assessment o~~f~~n the product should be included ~~where relevant~~, with reference to section 6.6.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
EFPIA	It would be helpful to receive more detailed guidance on how extensive the "conclusions on the environmental risk assessment" part should be. Like for e.g. the "Pregnancy" section, examples of wording to be used should be provided.	Beyond the scope of the present guideline.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

A list should be given of the excipients, expressed qualitatively only. All excipients, which are present in the product, should be included, even those present in small amounts, such as printing inks. Further details on the excipients to be declared may be found in the section on definitions and examples in the *Guideline on the Excipients in the Label and Package Leaflet of Medicinal Products for Human Use*. For transdermal patches, all ingredients of the patch (including the adhesive, release liner and backing film) should be mentioned.

The active substance itself, residues of substances used during manufacture of the finished product (for example, solvents, head-space gases or antibiotics in vaccine manufacture), lubricants for pre-filled syringes and constituents of capsule shells for inhalation powders not intended to be taken should not be included.

However, certain residues such as residues of antibiotic or other antimicrobial agents used in production that are known allergens with a potential for inducing undesirable effects should be mentioned in section 4.3 or 4.4 as appropriate.

Excipients should be referred to by their recommended INN if existing, accompanied by the salt or hydrate form if relevant or by their European Pharmacopoeia name. If an excipient has neither an INN nor European Pharmacopoeia name, it should be described by its usual common name. References to the pharmacopoeial quality should not be included. E numbers should be given ~~where they exist~~ along with the common name of the excipient where they exist and when necessary for proper use, e.g. when the excipient is listed in the Guideline on the excipients in the label and package leaflet of medicinal products for human use (as having recognised action or effect).

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
AESGP	With respect to foodstuffs, ingredients which are considered 'food' do not have E numbers, only the 'additives' and these are limited in number. Therefore it can be considered relevant to list E numbers for foodstuffs. However, in the case of human medicines almost all excipients are not foodstuffs (except sugars & a few other exceptions) and therefore the majority of excipients used in human medicines have E numbers. It is not meaningful for the prescriber or the patient to see all E numbers in the SmPC. It is also not practical to have a long list of E numbers in the SmPC. We therefore propose that 'relevant' E numbers be defined and only relevant E numbers be listed in the SmPC. Change the sentence to *"Relevant E numbers should be given where they exist along with the common name of the excipient."* Furthermore this new requirement would be in contrast to the German decree on excipients labelling (Bezeichnungsverordnung). This decree defines that E Numbers should not be mentioned, except excipients are listed in the annex of the *Guideline on the excipients in the label and the leaflet*.	See above revised wording.

The ingredients in excipient mixtures should be listed individually. In cases where the full composition of a flavour or fragrance is not known to the applicant or is too complex, it may be declared in general terms (e.g. 'orange flavour', 'citrus perfume'). However, any of the components, which are known to have a recognised action or effect ~~must~~should be included.

Ingredients that may or may not be added for the pH adjustment should be followed by the parenthesis '(for pH-adjustment)'

Invented names or general descriptive names such as 'printing ink' should not be used in place of the common name of an ingredient or of a mixture of ingredients but may be used in conjunction with the name(s) of the ingredient(s), so long as it is clear which ingredients are described by the name.

Chemically modified excipients should be declared in such a way as to avoid confusion with the unmodified excipients, e.g. 'pregelatinised starch'.

In the case of a product containing a covert marker for the purpose of tracking, tracing and authenti~~fi~~cation, a general term such as "authenti~~fi~~cation factor" should be included in the list of excipients instead of the name of the excipient, unless the excipient is one that is known to have a recognised action or effect.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
EFPIA	The requirement to use the term 'authentification factor' when a covert marker is being used does not provide any useful information to the prescriber. Such markers do not have pharmacological effects because they are used in very minute quantities (i.e., ppm or ppb) and are inert. In addition, it could potentially raise awareness to counterfeiters as to the	All excipients which are present in the product should be included in the SmPC even those present in small amounts. Guideline proposal

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	covert technology. Dispensation should be given from including covert markers in the list of excipients unless the excipient is one that is known to have a recognised action or effect. Suggested wording: *"Dispensation may be given from including covert markers in the list of excipients unless the excipient is one that is known to have a recognised action or effect."*	consistent with outcome of the 48th Meeting of the Pharmaceutical Committee on this matter.

For clarity, it is recommended that each excipient be listed on a separate line. It can be useful to list excipients according to the different parts of the product, e.g. tablet core/coat, capsule contents/shells, etc. For products that are presented in more than one container or in dual-chamber containers, the excipients should be listed per container or per chamber.

Abbreviations for excipients should not be used. However, where justified for space considerations, abbreviations for excipient names may appear on the labelling, on condition that these abbreviations are designated in section 6.1.

6.2 Incompatibilities

Information on physical and chemical incompatibilities of the medicinal product with other products with which it is likely to be mixed or co-administered should be stated. This is particularly important for medicinal products to be reconstituted and/or diluted before parenteral administration. Significant interaction problems, e.g. sorption of products or product components to syringes, large volume parenteral containers, tubing, in-line filters, administration sets, etc. should be stated.

Statements concerning compatibility of the product with other medicinal products or devices should not be included in this section but in section 6.6. Statements concerning pharmacological and chemical/physical incompatibilities with food should be included in section 4.5. If appropriate, the standard statement, 'Not applicable', should be included.

For certain pharmaceutical forms, e.g. parenterals, either of the following standard statements should be included as appropriate:

- *'In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.'*
- *'This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.'*

6.3 Shelf life

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
EFPIA	Shelf life: More detail is required here regarding temporary storage conditions, this may not be available for older products, so we question the expectation of this new guidance document on currently licensed products.	See answer to specific comment below and section on general principles

The shelf life should be given for the medicinal product as packaged for sale and, if appropriate, after dilution or reconstitution or after first opening ~~if appropriate~~.

A clear statement of the shelf life should be given, in an appropriate unit of time.

For statements to be included regarding in-use shelf lives of sterile products, consult the *Note for Guidance on maximum shelf life for sterile products for human use after first opening or following reconstitution*. An in-use shelf life may need to be stated for other medicinal products if development studies have found it to be necessary.

~~In a~~Additionally, if different concentrations ~~may~~ need to be prepared, ~~in particular~~ e.g. for use in~~for~~ children, the ~~chemical and physical~~ physicochemical stability ~~should be stated within~~ throughout the entire concentration range~~s~~ should be stated; e.g *"The ~~chemical and physical in use~~ stability has been demonstrated between x mg/ml and y mg/ml for t hours/days at 25 ºC and 2-8 ºC"*.

In case of a paediatric indication, if no age appropriate formulation is available for children but an extemporaneous formulation could be prepared from an existing adult formulation, relevant physicochemical data on storage and stability should be included here with a cross-reference in sections 6.4 and 6.6."

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
Pharmasy-mbiosis Ltd:	Please confirm if this statement refers to sterile and non sterile formulations? Suggested text: Additionally, if different concentrations need to be prepared, particularly for children, the chemical and physical stability throughout the entire concentration range must be stated e.g.	Agreed
EFPIA	This paragraph mentions "in particular for children, the chemical and physical stability should be stated." Why for children in particular? Why the chemical and physical stability? It seems that the "stability" only should be sufficient. The sentence should be further detailed as proposed in order to avoid the risk of change of container at the time of dilution. Change the sentence to: *"In addition, if a different concentration may need to be prepared, ~~in particular for children,~~ the stability should be stated within the concentration ranges; e.g "The ~~chemical and physical~~ in-use stability has been demonstrated between x mg/ml and y mg/ml for t hours/days at 25 ºC and 2-8 ºC in the original container-closure system (i.e. vial ...)"*.	Wording has been partly revised; see above.
AFSSAP/BWP	Reference to transport should be deleted because it may be misinterpreted.	Agreed, see below

In case of ~~different~~ specific temporary storage conditions need to be provided to healthcare professionals or patients, e.g. for the purpose of ~~transport and/or~~ ambulatory use (e.g. shelf-life 24 months at 2-8°C of which 3 months could be below 25°C), specific additional guidance should be provided as appropriate. Such information should always be based on stability data. In particular, the recommended temperature range and maximum duration of temporary storage should be specified. This guidance ~~should~~ may also include the action to be taken after the product has~~d~~ been stored under the temporary storage conditions (e.g. discard immediately).
Statements such as "These data are not recommendations for storage" should not be used.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
Pharmasy-mbiosis Ltd:	replace should by must as proposed above	Must is not suitable for guideline
Roche	The text about temporary storage conditions should be further clarified to avoid any misinterpretation about who it applies to. *In case ~~of different~~ specific temporary storage conditions are provided for the doctor or patient e.g. for the purpose of …*	Agreed
EFPIA	Delete the last two sentences about what action should be taken. If the temporary storage is called out, then the product is acceptable as long as it falls within the storage time. *"In particular, the recommended temperature range and maximum duration of temporary storage should be specified. ~~This guidance should also include the action to be taken after the product had been stored under the temporary storage conditions (e.g. discard immediately). Statements such as "These data are not recommendations for storage" should not be used.~~*	Sentences have been kept but "should" have been replaced by "may" in the first sentence.

No reference should be made to the container unless there are different shelf lives for different containers. Storage conditions should not be included, except for the storage conditions after opening (see the corresponding guideline). Statements such as 'Do not use after the expiry date' should not be included.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
MEB	We propose to mention this paragraph directly after the paragraph about the stability of different concentrations for children, because both paragraphs refer to storage and stability of preparations for children	Agreed; i.e. as 5th paragraph. See also comment below.
EFPIA	The inserted paragraph on paediatric indications gives guidance in development considerations in the final sentence: "Data on chemical stability are preferable, as microbiological stability will depend on numerous factors." This statement is outside the scope of this SmPC guidance and should be removed. Replace with: "In the case of a paediatric formulation, if no age appropriate formulation is available for children but an extemporaneous formulation is used, relevant data on storage should be included here with a cross-reference in 6.4." ~~Data on chemical stability are preferable, as microbiological stability will depend on numerous factors.~~	Agreed see above

~~In case of a paediatric indication, if no age appropriate formulation is available for children but an extemporaneous formulation is used~~could be prepared from an existing adult formulation~~, data on storage and stability should be included here with a cross-reference in s~~6.4 and 6.6. Data on chemical stability are preferable, as microbiological stability will depend on numerous factors.~~

When a device is supplied together with a medicinal product, the in-use shelf-life of the device should be given where applicable.

6.4 Special precautions for storage

Storage warnings should use one or more of the standard statements from the *Note for Guidance on declaration of storage conditions in the product information of medicinal products*. When such a standard statement is used, an explanation specifying whether the product is sensitive to light and/or moisture should be added.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
Pharmasy-mbiosis Ltd:	The statements provided in the guideline address whether a product is sensitive to light or moisture, so why is it necessary to add another standard statement?	It is not required to add a new statement but to add an explanation

For storage of sterile products that have been opened, diluted or reconstituted, a cross-reference should be made to section 6.3.

Note that if a specific storage warning is required, the warning should be consistent between the SmPC, label and PL.

A warning to keep the product out of the reach and sight of children should not be included in the SmPC.

6.5 Nature and contents of container

Reference should be made to the immediate container using the European Pharmacopoeia standard term; the material of construction of the immediate container should be stated ('glass vials', 'PVC/Aluminium blisters', 'HDPE bottles'); and any other component of the product should be listed, e.g. needles, swabs, measuring spoons, syringes inhaler devices, desiccant. The graduation on measuring devices should be explained~~The graduation of the measuring device should be stated~~. The container of any solvent provided with the medicinal product should also be described. Excessive detail, e.g., concerning the colour of the stopper, the nature of the heat-seal lacquer, should usually not be included. For parenteral preparations, when enclosure colour is used to differentiate between the presentations of a product, this should be stated here.~~In cases where the colour of a cap can be used to differentiate the different presentation of a parenteral product, it should be indicated here.~~

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
EFPIA	It is questionable whether the graduation of the measuring device should always be stated in the SmPC. We propose to add "as appropriate". The sentence would then read as follows: "The graduation of the measuring device should be stated,	Graduation should be explained.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	as appropriate".	

If appropriate, it should be indicated if the container closure is child-resistant.

Examples on the text in this section:

'<Volume> ml suspension in a pre-filled syringe (glass) with plunger stopper (chlorobutyl rubber) with or without needle in pack sizes of 5 or 10.'

'HDPE bottle with a child-resistant closure and a silica gel desiccant. Pack-sizes of 30, 60 or 90 film-coated tablets .'

All pack sizes should be listed. Pack sizes mentioned should include the number of units, number of doses (for e.g. multi-dose vaccines, inhalers, etc.), total weight or volume of the immediate container, as appropriate, and the number of containers present in any outer carton. If appropriate, a standard statement, 'Not all pack sizes may be marketed', should be included, in order to alert health professionals to the fact that not all listed pack sizes may be available for prescribing or dispensing.

Multiple unit packs for distribution purposes only do not constitute new pack sizes for marketing of the product and should therefore not be included in this section.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
Roche	It should be mentioned specifically if there is latex or not.	The material of construction of the immediate container should be stated.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product[2]

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
AESGP	The heading of section 6.6 is unnecessarily long and complicated. The heading as well as the content should follow a logical order of actions i.e. use, handling and disposal. Clarification on the content should be included within the SmPC guideline and the annotated QRD SmPC template. The QRD template already adequately covers this by recommending to: "[include practical considerations for preparation and handling of the product, where applicable including disposal of medicinal products and waster materials]". We propose: "Special precautions for use, handling and disposal"	Current heading covers both legal requirements and practical needs.
EFPIA	In case a medicinal product is used in conjunction with a specific medical device, a cross-reference in section 6.6 to a leaflet explaining the use of the device should be allowed.	Outside the scope of this guideline

[2] This section is reflected in the QRD template in the section 6.6 'Special precautions for disposal < and other handling >'

Instructions for disposal should be included here, if appropriate for the product.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
MEDEV /ESIP	Instructions for disposal should be included here. Not only if appropriate for the product. People are not really conscious how to handle pharmaceutical waste therefore it would be useful to give them information on this topic in all cases.	The SmPC is addressed to Healthcare Professionals. Disposals of medicines may differ between Members States. HCPs may therefore be better informed on standard method for disposal through other tools.

Where special precautions for the handling and disposal of certain products such as cytotoxics and some biological products or waste material derived from it are advised, e.g. in the case of products containing live organisms, these should be stated in this section, as should, where relevant, the disposal of items which come into contact with the product, such as nappies, or spoons used to administer oral vaccines. If relevant, a cross-reference to conclusions on the environmental risk assessment described in section 5.3 can be included.

If applicable, e.g. for cytotoxics, the following standard statement should be included, 'Any unused product or waste material should be disposed of in accordance with local requirements.'

If there are no special use or handling instructions for the pharmacist or other healthcare professionals, the standard statement, 'No special requirements.' should be included.

Any directions necessary for the accurate preparation of certain products such as cytotoxics and some biological products and/or necessary for the protection of persons including parents or carers preparing or handling the product should be stated.

In section 4.2, instructions on handling of the product by the doctor, other health personnel, or patient should be included, as well as general information concerning the administration of the product (whether administered by the patient or the health personnel). If instructions for use/handling are needed where the medicinal product has to be prepared before use, e.g. where it must be suspended or diluted, this information has to be given here.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
AESGP	We wonder what is the rationale for splitting of "instruction for handling" in section 4.2 and "preparation of administration" in 6.6 ? It is better for doctors to have all information in one place. The splitting causes that information is given twice – in sections 4.2 and 6.6.	Information may be relevant for doctors as well as other healthcare professionals (e.g. pharmacists). It is therefore important to ensure appropriate cross-reference to the two sections as proposed below.

For clarity, a cross-reference in section 4.2 to the relevant information in section 6.6 could be included, e.g. 'For instructions on dilution of the product before administration, see section 6.6.'

It is recommend that only information necessary for the pharmacist or other health personnel to prepare the product for administration to the patient should be included here.

Information on the preparation (e.g. the suspension of a powder for injection, or preparing a dilution) of the medicinal should be included in section 6.6, regardless of who prepares the product (e.g. pharmacist, doctor, other health personnel, patient, parents or carers). In the case of products for reconstitution, the appearance of the product after reconstitution should be stated.

Statements concerning compatibility of the product with other medicinal products or devices can be given here provided the data have been provided in the dossier.

In the exceptional cases where a product is indicated in children and where no adequate paediatric formulation can be developed (based on duly justified scientific grounds)~~where information on an extemporaneous formulation for paediatric use is necessary~~, ~~it~~information on extemporaneous formulation should appear under a sub-heading "*Use in the paediatric population*" and should cross-refer to the section 4.2. Detailed instructions for the preparation of the extemporaneous formulation from the appropriate "adult" or other "older children" dosage form and additional information on extemporaneous formulations for use in younger children shall be provided and, where appropriate, the maximum storage time during which such preparation will conform to its specifications. When necessary, the required packaging material and storage conditions should be stated here.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
Pharmasy-mbiosis Ltd	information on extemporaneous preparations is inappropriate as they are unlicensed mediciens	See revised wording.
MHRA, Vigilance and Risk Management of Medicines Division	Inclusion of instructions for extemporaneous preparation should be severely restricted to the most exceptional cases e.g. where necessary to ensure that a particular medicine can be given to children in the event of a flu pandemic. We are concerned that the phrase 'exceptional' will allow MA holders to avoid developing formulations which are suitable for children if it is interpreted too widely – in contrast to the stated objectives of the EU Paediatric Regulation. Consideration should be given to strengthening the wording of this paragraph both here and in Section 4.2 to make the nature of the exceptional case clearer.	Agreed, see revised wording.
EFPIA	It is questionable whether this entire paragraph relating to extemporaneous formulation for paediatric use is positioned in the appropriate section and should be moved to section 4.2. Move paragraph 9 to a more suitable location e.g. section 4.2.	Direction for preparation and handling of the product is described in this section. Furthermore, there will be in section 4.2 a cross-reference to this section.

Any specific warnings for the handling of the product should be in section 4.4.

Information on risks due to occupational exposure should be included in this section, with reference to section 4.4 or 4.8 if there is information in that section.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
MHRA	Relevant ERA conclusions are to be included in section 5.3 with reference to section 6.6 but there appears to be nothing in the guidance for section 6.6 mentioning inclusion of relevant ERA information and no reference back to section 5.3. Include	Section 6.6 may describe special precautions for disposal and other handling of the product which could be required following an

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	guidance on ERA in section 6.6.	ERA. The possibility to have a cross reference to 5.3 has been added.

7 MARKETING AUTHORISATION HOLDER

Name and permanent address or registered place of business of the Marketing Authorisation Holder. Telephone, fax numbers or e-mail addresses may be included (no websites or emails linking to websites).

8 MARKETING AUTHORISATION NUMBER(S)

Item to be completed by the competent authority or by the Marketing Authorisation Holder once the Marketing Authorisation has been granted. For medicinal products for which the European Commission is the Competent Authority, the number to be included in this section is the number in the Community Register.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
MEDEV / ESIP	The presentations listed in this section must be unambiguously identifiable. Product name, strength, pharmaceutical form, package size and container are essential information.	Comment acknowledged

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Item to be completed by the competent authority or by the Marketing Authorisation Holder once the Marketing Authorisation has been granted or renewed. Both the date of first authorisation and, if the authorisation has been renewed, the date of the (last) renewal should be stated in the format given in the following example:

Date of first authorisation: 3 April 1985

Date of latest renewal: 3 April 2000

~~***Information related to the authorisation:***~~

~~•*[For products approved under 'conditional approval' in the centralised procedure, include the following statement:]*~~

~~<This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency (EMEA) will review new information on the product every year and this SmPC will be updated as necessary.>~~

~~•*[For products approved under 'exceptional circumstances', include the following statement:]*~~

~~<This medicinal product has been authorised under 'Exceptional Circumstances'. This means that <due to the rarity of the disease> <for scientific reasons> <for ethical reasons> it has not been possible to obtain complete information on this medicinal product. The {name of Agency} will review any new information which may become available every year and this SmPC will be updated as necessary.>~~

~~•***Paediatric investigation Plans***~~

~~*[If the a deferral of the initiation or completion of measures included in a paediatric investigation plan has deferral has been decided, it should be stated as follows:]*~~

~~<In accordance with the Paediatric Regulation, <<initiation><completion> of studies in the paediatric investigation plan of <x> to be performed in children from the age of x to y years/months has been deferred because <it was considered appropriate to conduct studies in adults prior to initiating studies in the paediatric population> <studies in the paediatric population would take longer to conduct than studies in adults><additional non-clinical data were considered necessary><major quality problems prevented development of the relevant formulation(s)>.>~~

~~Cross-reference to this information may be included in the clinical particulars, e.g. 4.2 to provide a complete overview of available experience in all subset of the paediatric population.~~

~~*[If the product has received a waiver of paediatric development, the information should be given as follows:]*~~

~~<In accordance with the Paediatric Regulation, the development of <X> in children from the age of x to y years has been waived because :~~

~~- <<x> is likely to be ineffective or unsafe <in this subset of the paediatric population> <in all subsets of paediatric population> >~~

~~- <the authorised indication does not occur in the paediatric population>~~

~~- <the use of <x> is not expected to bring significant therapeutic benefit~~

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
Roche	This section should include only dates and no details on the authorisation. Conditional approval and exceptional circumstances: move to another section (e.g. section 5) or to the end of the SmPC. Paediatric investigation plans: move to another section (e.g section 4).	Proposed statements on waiver and deferral have been simplified and put back in section 5.1.
MEB:	Deletion of second bullet point See our comment in section 4.2	See section 5.1
AESGP	Article 8 of the paediatric Regulation requires only that any waiver or deferral which has been granted is recorded in the SmPC, not that reasons for the deferral or waiver should be given. There may be a wide range of reasons for a deferral or waiver and these are unlikely to fall into the simple categories proposed in this section. A simpler statement would be more appropriate especially as Paediatric Committee opinions are published on the EMEA web-site (to which the reader could be referred) Change the text relating to waivers or deferrals to: *"[If a deferral of the initiation or completion of measures included in a paediatric investigation plan has been decided, it should be stated as follows:]* <In accordance with the Paediatric Regulation, <<initiation><completion> of studies in the paediatric investigation plan of <x> to be performed in children from the age of x to y years/months has been	Taken into account; see section 5.1.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	deferred. *[If the product has received a waiver of paediatric development, the information should be given as follows:]* <In accordance with the Paediatric Regulation, the development of <X> in children from the age of x to y years has been waived."	
EFPIA	The paediatric Regulation article 8 requires only that any waiver or deferral which has been granted is recorded in the SmPC, not that reasons for the deferral or waiver should be given. There may be a wide range of reasons for a deferral or waiver and these are unlikely to fall into the simple categories proposed in this section. A simpler statement would be more appropriate especially as Paediatric Committee opinions are published on the EMEA web-site Change the text relating to waivers or deferrals to: *If a deferral of the initiation or completion of measures included in a paediatric investigation plan has been decided, it should be stated as follows:]* <In accordance with the Paediatric Regulation, <<initiation><completion> of studies in the paediatric investigation plan of <x> to be performed in children from the age of x to y years/months has been deferred. *[If the product has received a waiver of paediatric development, the information should be given as follows:]* <In accordance with the Paediatric Regulation, the development of <X> in children from the age of x to y years has been waived.	Taken into account; see section 5.1.

10 DATE OF REVISION OF THE TEXT

Leave blank in case of a first Marketing Authorisation.

For medicinal products for which the European Commission is the Competent Authority: date of approval of latest variation or transfer, e.g. the latest Commission Decision amending the SmPC, implementation date of the Urgent Safety Restriction or date of (EMEA) notification amending the annexes to the Marketing Authorisation.

For products for which Member States are the Competent Authorities: date of approval of latest variation or implementation date of the Urgent Safety Restriction resulting in a revision of the SmPC.

Item to be completed by the competent authority or by the Marketing Authorisation Holder at time of printing the SmPC.

11 DOSIMETRY (IF APPLICABLE)

Full details of internal radiation dosimetry should be included in this section for radiopharmaceuticals. For all other products, this section should be excluded.

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

For radiopharmaceuticals, additional detailed instructions for extemporaneous preparation and quality control of such preparation and, where appropriate, maximum storage time during which any intermediate preparation such as an eluate or the ready-to-use pharmaceutical will conform to its specifications.

Special instructions relating to the disposal of containers and unused contents should also be included.

Annexes 1 and 3 have been taken out of the SmPC guideline since examples of standard statements should be considered together with the assessment of data on reproduction and lactation. They should therefore be read in conjunction with the CHMP/SWP guideline on reproduction and lactation to which they are annexed.

Comments received on those annexes were forwarded to SWP for their consideration when finalising the revision of this guideline

~~**ANNEX 1:** EXAMPLE WORDING FOR SECTION 4.6 PREGNANCY~~

~~Revision as proposed by SWP~~

~~[1]~~ ~~< Based on human experience *(specify)* <{Active substance} causes congenital malformations *(specify)* when administered during pregnancy.~~
~~*[or]*~~
~~causes harmful pharmacological effects during pregnancy and/or on the foetus/new-born child.>~~
~~{Invented name} is contraindicated <during pregnancy><during {trimester} of pregnancy> *[this case is a strict contraindication]* (see section 4.3) >~~
~~*[or]*~~
~~{Invented name} should not be used <during pregnancy> <during {trimester} of pregnancy>~~
~~<Women of childbearing potential have to use effective contraception <during <and up to {number} weeks after)> treatment.>>~~

~~[2]~~ ~~< Based on human experience *(specify)* {Active substance} <is suggested / suspected to cause congenital malformations *(specify)* when administered during pregnancy.~~
~~*[or]*~~
~~A <Studies in animals have shown reproductive toxicity (see section 5.3).>~~
~~*[or]*~~
~~B <Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).>~~
~~{Invented name} is contraindicated <during pregnancy><during {trimester} of pregnancy> *[this case is a strict contraindication]*. (see section 4.3) >~~
~~*[or]*~~
~~{Invented name} should not be used<during pregnancy><during {trimester} of pregnancy>~~
~~<Women of childbearing potential have to use effective contraception <during <and up to {number} weeks after)> treatment.>>~~

~~[3]~~ ~~< Based on human experience *(specify)* {Active substance} <is suggested / suspected to cause congenital malformations *(specify)* when administered during pregnancy.~~
~~*[or]*~~
~~Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).~~
~~<{Invented name} is not recommended / should not be used > <in pregnancy > <during {trimester} of pregnancy > and in women of childbearing potential not using effective contraception, unless the clinical condition of the woman requires treatment with {active substance} >~~

~~[4]~~ ~~<There are no or limited amount of data from the use of {Active substance} in pregnant women>~~
~~A <Studies in animals have shown reproductive toxicity (see section 5.3).>~~
~~*[or]*~~
~~B <Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).>~~
~~{Invented name} is not recommended / should not be used < during pregnancy > <during {trimester} of pregnancy > and in women of childbearing potential not using effective contraception >~~

~~[5]~~ ~~<There are no or limited amount of data from the use of {Active substance} in pregnant women>~~
~~Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).~~

As a precautionary measure, it is preferable < to avoid the use of {invented name} <during pregnancy > <during {trimester} of pregnancy >.

[6] A fair amount of data on pregnant women indicate no malformative or feto/ neonatal toxicity of {Active substance}.
A <Animal studies have shown reproductive toxicity (see section 5.3). *[or]*
B <Animal studies are insufficient with respect to reproductive toxicity (see section 5.3)>.
As a precautionary measure, it is preferable < to avoid the use of {invented name}> <during pregnancy > <during {trimester} of pregnancy >

[7] A fair amount of data on pregnant women indicate no malformative or foeto/ neonatal toxicity.
Animal studies do not indicate reproductive toxicity (see section 5.3).
The use of {invented name} may be considered <during pregnancy > <during {trimester} of pregnancy >, if necessary.
[8] A large amount of data on pregnant women indicate no malformative nor foeto/ neonatal toxicity.
{Invented name} can be used <during pregnancy > <during {trimester} of pregnancy >

[9] No effects during pregnancy are anticipated, since systemic exposure to (Active substance) is negligible.

(Invented name) can be used during pregnancy. *(E.g. drugs for which negligible systemic exposure/negligible pharmacodynamic systemic activity has been demonstrated in clinical situation)*

ANNEX ~~2~~

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
Alcon Laboratories	The SOC order is different from that stated in APPENDIX II MedDRA (version 8.2) terminology to be used in section 4.8 "undesirable effects" of the SPC. As updates of MedDRA and consequently the QRD guidance documents occur more frequently than revisions to the SPC guidelines it might be appropriate to add a statement to the SOC list advising consultation with current MedDRA and QRD guidelines at the time of generating the SPC.	The current discrepancy between the SmPC guideline and the QRD template providing the translation of the MedDRA SOCs is acknowledged. The later presents the list of SOCs in accordance with a more recent version of MedDRA. This discrepancy was questioned by few parties in the past and therefore, carefully considered during the preparation of the revision of the SmPC guideline. As a result, it was recommended not to change the current order as presented in the SmPC guideline because it is more "clinically relevant" and because order has to be kept standardised as much as possible in order that healthcare professionals become use to it. After finalisation of the revision of the SmPC guideline, the QRD template will be put in line. See also general comment from MedDRA Maintenance and Support Services Organization
CS QRD	ANNEX 2 APPENDIX II Currently, the attachment is called APPENDIX II	Confusion with QRD template
EFPIA	The MedDRA system organ class order in Annex 2 is still not consistent with the QRD template Provision of a definite order of SOCs is appreciated; however, it is strongly recommended to then use always the agreed order and not to change it whenever MedDRA takes a new approach.	See above

THE MEDICAL DICTIONARY FOR REGULATORY ACTIVITIES TERMINOLOGY (MedDRA)

All ADRs should be grouped according to the following order based on the MedDRA system organ classes (SOC). As a general rule, MedDRA terms should be classified according to the most relevant SOC related to the target organ.

A pragmatic approach to the location of terms should be taken in order to make the identification of adverse reactions simpler and clinically appropriate for the reader. For example, it may be helpful on some occasions – solely in the context of the SmPC - to use secondary SOC locations of some MedDRA Preferred Terms (PT), or sometimes to use locations that do not strictly accord with the MedDRA architecture. For example, if the PT ~~terms~~ '*Liver function test abnormal*', '*Hepatitis*' and '*Hepatic encephalopathy*' are to be included in an SmPC, it would be acceptable to include them all under the SOC '*Hepato-biliary disorders* ~~SOC~~' instead of distributing the reactions among the SOC '*Hepato-biliary disorders*', '*Nervous system disorders*' and '*Investigations*' ~~System Organ Classes'~~ as dictated by their primary location in MedDRA.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
MEDDRA MSSO	Change 'Hepato-biliary' to 'Hepatobiliary'; the word 'hepatobiliary" is unhyphenated in MedDRA. Also, use the full SOC name 'Hepatobiliary disorders' per MedDRA conventions, rather than using the abbreviated form 'Hepatobiliary SOC'. Also consider using the convention for MedDRA terms in text, namely; the level followed by the term in italics, without any quotation marks, e.g. SOC *Hepatobiliary disorders* Existing text: For example, if the terms 'Liver function test abnormal', 'Hepatitis' and 'Hepatic encephalopathy' are to be included in an SmPC, it would be acceptable to include them all under the 'Hepato-biliary SOC' instead of distributing the reactions among the 'Hepato-biliary disorders', 'Nervous system disorders' and 'Investigations System Organ Classes' as dictated by their primary location in MedDRA. For example, if PT *Liver function test abnormal*, PT *Hepatitis* and PT *Hepatic encephalopathy* are to be included in a SmPC, it would be acceptable to include them all under SOC *Hepatobiliary disorders* instead of distributing the reactions among SOC *Hepatobiliary disorders*, SOC *Nervous system disorders* and SOC *Investigations* as dictated by their primary location in MedDRA.	Agreed

SOC LIST

- Infections and infestations
- Neoplasms benign, malignant and unspecified (including cysts and polyps)
- Blood and ~~the~~ lymphatic system disorders
- Immune system disorders
- Endocrine disorders
- Metabolism and nutrition disorders
- Psychiatric disorders
- Nervous system disorders
- Eye disorders
- Ear and labyrinth disorders
- Cardiac disorders
- Vascular disorders
- Respiratory, thoracic and mediastinal disorders
- Gastrointestinal disorders

- Hepato-biliary disorders
- Skin and subcutaneous tissue disorders
- Musculoskeletal and connective tissue disorders
- Renal and urinary disorders
- Pregnancy, puerperium and perinatal conditions
- Reproductive system and breast disorders
- Congenital, and familial/ and genetic disorders
- General disorders and administration site conditions
- Investigations
- Injury, poisoning and procedural complications
- Surgical and medical procedures
- Social circumstances

ADR Adverse reaction descriptions should be based on the most suitable representation within the MedDRA terminology. This will usually be at the PT level, although there may be instances where the use of Lowest Level Terms (LLT) or group terms, such as high-level terms (HLT) may be appropriate. It is acceptable to adapt the names of the MedDRA group terms if this makes their meaning more transparent to the reader of the SmPC; e.g. the HLT *Genitourinary tract disorders NEC*, if otherwise appropriate for the SmPC under consideration, could be presented without the suffix 'NEC'. The use of the suffixes NEC and NOS are not appropriate for inclusion in the SmPC. The adverse reaction term should be expressed in natural word order, e.g. 'Interstitial pneumonia' in preference to 'Pneumonia interstitial'. It may be appropriate to modify MedDRA terms in other ways in the interests of comprehensibility. The most widely recognised term for a particular condition should be used, e.g. the use of LLT 'Churg Strauss syndrome' might be more appropriate than the PT the use of 'Allergic granulomatous angiitis'.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
MEDDRA MSSO	The example provided, HLT *Genitourinary tract disorders NEC,* is an HLGT in the current version of MedDRA, not an HLT. We suggest replacing with HLT *Renal disorders NEC* as the example of an HLT. Existing text: e.g. the HLT *Genitourinary tract disorders NEC* Proposed text: e.g. the HLT *Renal disorders NEC*	See above simplification

Within each MedDRA SOC, ADRs adverse reactions should be classified according to their frequency of occurrence. Prior to estimating frequency of occurrence of adverse events from systematic studies (clinical trials or other sources), appropriate levels of the MedDRA hierarchy should be used in order to group together clinically related conditions in a meaningful way. For example, if 'postural dizziness', 'exertional dizziness' and 'unspecified dizziness' were each reported by 2% of patients, this might reasonably be represented in the SmPC as 'Dizziness' occurring in 6% of patients (assuming that only one report of dizziness applied to each patient). It may also be appropriate to use *ad hoc* groupings of terms, or to adapt MedDRA group terms if the established MedDRA group terms are not completely suitable, e.g. reports of adverse reactions represented as the MedDRA PT 'Diarrhoea', 'Diarrhoea aggravated', 'Loose stools', 'Stools watery', and 'Intestinal hypermotility' or other are present in MedDRA under 3 separate HLT – 'Diarrhoea (excl infective)', 'Gastrointestinal spastic and hypermotility disorders' and 'Faeces abnormal'. These HLTs may not be useful for representing the findings in the SmPC. In the interests of making the SmPC relevant and comprehensible to clinicians, these might all reasonably be represented as the single term 'Diarrhoea' in the interest of making the SmPC relevant and comprehensible to patients., and tThe total number of those cases with the respective MedDRA PT counted together in order should be used to estimate the frequency of diarrhoeaoccurrence.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
MEDDRA MSSO	Diarrhoea aggravated, Loose stools and Stools watery are not PTs in the current version of MedDRA; they are all LLTs linking to PT Diarrhoea. Intestinal hypermotility is not a PT in the current version of MedDRA; it is an LLT mapping to PT *Gastrointestinal hypermotility*. Furthermore, Gastrointestinal hypermotility is seen as a distinct concept and we do not think it is clinically appropriate to group it with diarrhoea concepts. Faeces abnormal is not an HLT in the current version of MedDRA. There is HLT Faecal analyses NEC but none of the terms cited map to this HLT. Therefore, we suggest updating the 'Diarrhoea' example with the text in the Proposed Change column. Existing text: It may also be appropriate to use *ad hoc* groupings of terms, or to adapt MedDRA group terms if the established MedDRA group terms are not completely suitable, e.g. reports of adverse reactions represented as the MedDRA PT 'Diarrhoea', 'Diarrhoea aggravated', 'Loose stools', 'Stools watery', and 'Intestinal hypermotility' are present in MedDRA under 3 separate HLT – 'Diarrhoea (excl infective)', 'Gastrointestinal spastic and hypermotility disorders' and 'Faeces abnormal'. These HLTs may not be useful for representing the findings in the SmPC. In the interests of making the SmPC relevant and comprehensible to clinicians, these might all reasonably be represented as the single term 'Diarrhoea', and the total number of cases with the respective MedDRA PT counted together in order to estimate frequency of occurrence. Proposed text: It may also be appropriate to use *ad hoc* groupings of terms, or to adapt MedDRA group terms if the established MedDRA group terms are not completely suitable, e.g. reports of adverse reactions represented as PT *Diarrhoea*, PT *Diarrhoea bacterial*, and PT *Viral diarrhoea* are present in MedDRA under 3 separate HLTs – HLT *Diarrhoea (excl infective)*, HLT *Bacterial infections NEC*, and HLT *Viral infections NEC*. These HLTs may not be useful for representing the findings in the SmPC. In the interests of making the SmPC relevant and comprehensible to clinicians, these might all reasonably be represented as the single term 'Diarrhoea', and the total number of cases with the respective MedDRA PT counted together in order to estimate frequency of occurrence.	See above simplification
Pharmaceuti-cs LLC	This example has been (wrongly) interpreted to mean that concept-lumping for the purposes of frequency calculation does not have to involve clinical interpretation. However, the opposite is true, and -translated into this example - the recommendation would be to lump the concept "postural dizziness" together with reports of postural hypotension, and to lump reports of "exertional dizziness" together with other events that represent, e.g., cardiac insufficiency - provided	Such a representation illustrates a specific example and may not necessarily apply to all such situations and will depend on the scientific safety assessment.

ORGANISA-TION	COMMENT(S)	OUTCOME/ CONCLUSION
	that these two phenomena are considered undesirable effects. What is shown in this example is only possible when the author of labeling has strong reasons to ignore the "mechanism attribution" of dizziness by the investigator/reporter. We believe that this example was never meant to encourage uncritical term lumping. Replace the 3 dizziness concepts by PTs that represent the 3 concepts used in revised 4.8 to illustrate the same issue: sedation, somnolence, drowsiness. Here is the context from 4.8: "Reactions that are reported under different terms but represent the same phenomenon (e.g., sedation, somnolence, drowsiness) should ordinarily be grouped together as a single adverse reaction to avoid diluting or obscuring the true effect."	