9 October 2017
EMA/CHMP/157146/2015
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on the draft 'Questions and answers on cyclodextrins' (EMA/CHMP/495747/2013)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	IFAPP (International Federation of Associations of Pharmaceutical Physicians & Pharmaceutical Medicine)
2	EFPIA – Sylvie Meillerais (sylvie.meillerais@efpia.eu)
3	AESGP (represents the manufacturers of non-prescription medicines in Europe)
4	Merck Sharp & Dohme
5	ROQUETTE FRERES
6	Medicines Evaluation Board in The Netherlands
7	Bioresco Ltd.

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
2	EFPIA welcomes the opportunity to contribute to this Q&A and would like to comment on the overall context, i.e. the revision of the GL on 'Excipients in the label and package leaflet of medicinal products for human use'. The intent of this guidance is to provide advice to patients and prescribers. In order for labelling on cyclodextrins (CDs) to have a beneficial outcome in the prescriber environment, it is critically important that the advice provided is specific and actionable by patients and their prescribers. Therefore, EFPIA does not support general and non-specific warnings associated with a specific excipient. It is an important principle that warnings, especially, directed to patients should be as specific as possible and actionable. This current draft does not satisfy this need, to provide advice which a patient or prescriber can readily interpret and take action upon. EFPIA does support on the other hand the practice to disclose an excipient of concern in section 6 of the SmPC, but in case warnings, precautions and other usage advices are proposed in the SmPC, these should be made as specific as possible.	The updated warnings are more specific. See final wording.
2	**Concerns regarding scientific justifications:** 1. Zero thresholds for all routes of administration 2. Confusing presentation with respect to concentration (%) and administered dose 3. Unnecessarily precautionary advice to patients and prescribers with respect to paediatrics	

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	4. Interaction with other medicinal products 1) Zero thresholds for all routes of administration Zero thresholds are not supported by the known toxicology or toxicokinetics of the CDs, as provided in the materials presented (see Table 6). The presented hazards (diarrhoea, renal changes and risk of irritation) are only manifest at high doses, and there is sufficient evidence to postulate, in medicinal use scenarios, that thresholds exist. 2) Confusing presentation with respect to concentration (%) and administered dose It would be useful to have the context of CD listed as a quantity (mg) AND as a concentration so that the content of CD can be directly compared to the stated concerns (which are % or quantity based). This would allow the use of warning texts to be better linked to quantity / % and not be driven from a zero threshold. 3) Unnecessarily precautionary advice to patients and prescribers with respect to paediatrics The document states that “the presence of cyclodextrins should be stated as a precaution (zero thresholds)” (line 124) and instructs carers to check with the doctor “as the cyclodextrin contained in this medicine might cause undesirable effects” (line 128). This text seems to be precautionary and to raise concerns for patients and carers that may not be relevant.	1) This is agreed. However, using thresholds is a very complicating issue for cyclodextrines because of the complex behaviour of these excipients. Based on animal studies and human experience, harmful effects of CDs are surely not to be expected at doses below 20 mg/kg/day. Therefore, we suggest to use this threshold for all cyclodextrines for showing the amount of cyclodextrin and a warning that there is not enough information on children less than 2 years old. 2) It is indeed confusing to use both % and mg. We suggest to only use mg/kg/day. 3) This is agreed. The risks of CDs depend on the products, thus the products should be checked, and risks of the complete products should be stated in the SmPC. This is accordingly changed in the Q&A.

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	For example, will the medicine prescribed not have been studied in patients of the age-group being prescribed to? If so, doesn't this mean that the presumed risk has been evaluated during the investigational phase and hence the statement on checking risk is essentially redundant? <u>4) Interaction with other medicinal products</u> We understand that the aspect of interaction with other actives could be considered a potential risk but are concerned that the information might not be easily understood by prescribers or patients / care givers and might be taken as a more general concern than may in fact be appropriate or necessary. How, for example, would a prescriber know what interactions to manage against? It is not clear that all interactions of CDs that are asked to be stated in the SmPC will truly be known, especially across the wide range of possible active substances that may be being taken by a patient at the same time. Furthermore, it is our understanding that not all active substances will have similar levels of interaction with a CD complexing agent (and there may be some differences within the class of CDs). This is because the complexing interaction (average binding to a CD) is structurally-dependent. In addition, our understanding of the use of CDs is that they are employed to gain solubility of an active substance in a solution product (by forming equilibrating complexes with the active substance), often for IV delivery. For this reason it may be more pertinent to focus the precautionary statements on genuine co-administered materials in the clinical setting (e.g. in a single intravenous giving line). The dynamic equilibrium of drug active moiety with a CD combined with the	4) This is agreed. The CD changes the properties of the active substance, and thus the property of the product. Interactions of the product with other products should thus be written in the SmPC. It seems not reasonable to summarize all possible interactions of CDs with other compounds. Complexation of CDs with other drugs in the (blood)system seems indeed not to be the point. But the effect of CDs on e.g. dermal penetration of other drugs/substances might be important. And product-specific. The issue can be solved in the Q&A by the comment "*Safety aspects of CDs have been considered during the development and safety assessment of the drug product, and are clearly stated in the SmPC*".

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	considerable dilution of drug in blood after administration (and the low free drug levels that may result from protein binding) would all be considered to contribute to minimising complexation of other drugs. An issue might exist under extreme cases – e.g. with long term continuous infusion of CD and high blood levels of the CD; but this is an extremely limited scenario, and does not warrant the general and non-specific warning that is proposed.	
3	**Comments on oral administration of parent Cyclodextrins (alpha-, beta-, gamma-CD):** Parent CDs have been sufficiently investigated. As excipients in medicinal products they have no recognized action or effect. Oral administration is well tolerated and is not associated with any observable adverse effects (Loftsson and Brewster 2010) up to high dose levels. It is generally accepted that excipients may show effects above a certain dose. The cyclodextrin contents in marketed medicinal products, however, are far below possibly harmful concentrations that would require any specific warning. Therefore, it is not reasonable to establish a threshold “zero” for orally applied parent CDs. The intended wording for PIL/SPC concerning the amount of CDs, possible interactions and adverse events, is not justified by any concrete warning or instruction for action, neither for patients nor for doctors. In contrast to other ingredients as examples, also specific consequences in special patient groups, like in allergic persons (e. g. soya oil), patients with a special intolerance (e. g. lactose), patients with special diseases (e. g. maltitol for diabetics) or high-risk groups (e. g. ethanol for patients with liver diseases) are not defined. Thus, the intended wording may even be confusing for prescribers and patients, because it does not provide relevant and substantial warning statements necessary before taking the medicinal	It is agreed that a threshold of zero should not be used. Also, the risk-assessment should have been made on the total product, including the CD. However, there are insufficient data on children less than 2 years old, so from a significant amount of CD, like > 20 mg/kg, some attention should be taken. The text has been changed accordingly. The cited information is in agreement with the Background review for cyclodextrins.

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	product or a precise information how to use the product safely. The following comments refer to the oral administration of parent cyclodextrins (α-CD, β-CD and γ-CD). As the PDE-values given in the EMA document ("Background review for cyclodextrins used as excipients", November 2014) for the 3 parent CDs vary from 10 to 200 mg/kg b.w., toxicological data are discussed exemplarily for the parent CD with the lowest PDE-value, i. e. beta-cyclodextrin. The parent CDs alpha- and beta-cyclodextrin, are listed in a number of pharmacopoeial sources, including Ph.Eur., USP/NF and JPC. All three parent CDs were included in the GRAS list of the FDA. Orally administered parent CDs of pharmaceutical interest are practically non-toxic due to lack of absorption from the gastrointestinal tract (oral bioavailability in rats: alpha-CD 1%, beta-CD 0.6%, gamma-CD 0.02%). The absorbed CDs are essentially excreted in the urine without undergoing significant metabolism (Stella and He 2008). In normal volunteers after administration of 10 g in a fasting state or after 3 doses of 10 g daily with meals, insignificant levels of beta-CD were detectable in faeces. In ileostomy subjects, the recovery of beta-CD in the ileal effluent was 97±10% and 91±5% respectively. It was concluded that beta-CD is hardly hydrolyzed or absorbed in the human small intestine but is fermented by colonic microflora with minimal apparent hydrogen production (Flourié et al. 1992). A standard battery of toxicological studies performed with parent CDs confirm their low systemic toxicity: The LD50 of orally applied beta-CD is 19 g/kg b.w. in rats (Brewster and Loftsson 2007) or >5000 mg/kg b.w. in dogs (Sebestyén 1980). The NOAEL in 1-year studies in rats and dogs was 650 and 470 mg/kg b.w./day, respectively. At higher doses there were	

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	minor adverse effects (HRC 1994a, b). The NOAEL was between 560 and 2900 mg/kg b.w./day (depending on study stage) in a 3-generation reproductive toxicity study in rats, in which the only adverse effect seen at higher doses was impaired pup growth during lactation, probably secondary to reduced food consumption in the dams at this dose level. A 52-week toxicity study in dogs determined the non-toxic effect level of beta-CD after oral administration to be about 2 g/kg b.w./day (Bellringer et al. 1995). In a well-designed and properly conducted (Blumenthal et al. 1990) 90-day study in Sprague-Dawley-derived OFA rats, beta-CD appeared to lack toxicological activity at the doses of approx. 4.4 g/kg b.w./day and 5.3 g/kg b.w./day for males and females respectively (Olivier et al. 1991). From a 13-weeks study in dogs a NOAEL of 1234 mg/kg b.w./d was calculated. In the absence of any treatment-related macroscopic or microscopic pathological findings, the other effects noted were indicative of only a mild toxic response (Smith et al. 1992). The tolerance of orally administered gamma-CD was examined in a double-blind, placebo-controlled, crossover study in 24 healthy volunteers. It was found that a single dose of 8 g gamma-CD is well tolerated; 8 g gamma-CD or 8 g maltodextrin (placebo) did not reveal any differences in gastrointestinal tolerance of these two oligosaccharides. Two subjects reported flatulence, which is a frequent consequence of the consumption of malabsorbed carbohydrates, after placebo and test treatment (Koutsou et al. 1999). In another crossover study with healthy adult subjects (N = 32) 50 g of carbohydrate from gamma-CD effectively lowered postprandial glycemia and insulinemia compared with a rapidly digested maltodextrin, without resulting in appreciable carbohydrate malabsorption or gastrointestinal intolerance (Asp et al. 2006). In a human tolerance study, eighteen healthy males, aged 23±2 years,	

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	were given doses of 0, 24 or 48 g beta-CD/day in three successive periods of one week. There was a significant increase in complaints of flatulence ($p<0.05$) at the higher intake level; other scores of abdominal complaints, reported defaecation patterns and breath hydrogen did not change significantly. Thus, the dose of 24 g beta-CD/day was well tolerated on a short term basis (van Dokkum & van der Beek 1990). In addition, it should be considered that many orally applied medicinal products containing cyclodextrins as excipients, e. g. cough and cold preparations, are intended for short-term use. Therefore, data from safety studies like subchronic toxicity studies and data from human tolerance studies are of even higher relevance in regard to a safe short-term use. Thus, the "Background review for cyclodextrins used as excipients" (EMA 2013) comments: "The safe treatment time is considered to be at least 3 weeks, but presumably much longer."	
3	**Additional references:** ASP ML, HERTZLER SR, CHOW J, WOLF BW: Gamma-cyclodextrin lowers postprandial glycemia and insulinemia without carbohydrate malabsorption in healthy adults. J Am Coll Nutr 2006, 25(1): 49-55 BLUMENTHAL H, FLAMM WG, FORBES A, MUNRO I: Unpublished report of a Science Advisory Group convened to review data on toxicity and food applications of ß-cyclodextrin (1990) FLOURIÉ B, MOLIS C, ACHOUR L, DUPAS H, HATAT C, RAMBEAUD JC: Digestibility of ß-cyclodextrin in the human intestine. Unpublished report of INSERM U 290 (1992) HANUMEGOWDA UM, WU Y, ADAMS SP:	Acknowledged.

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	Potential Impact of Cyclodextrin-Containing Formulations in Toxicity Evaluation of Novel Compounds in Early Drug Discovery. J Pharmaceu Pharmacol. 2014;2(1): 5 HRC: Beta-cyclodextrin: Toxicity to rats by dietary administration for 52 weeks. Unpublished report no. ROQ 4/931090 from Huntingdon Research Centre Ltd, Huntingdon, Cambridgeshire, UK (1994a) HRC: Beta-cyclodextrin: Toxicity to dogs by repeated dietary administration for 52 weeks. Unpublished report no. ROQ 3/931848 from Huntingdon Research Centre Ltd, Huntingdon, Cambridgeshire, UK (1994b KOUTSOU GA, STOREY DM, BAR A: Gastrointestinal tolerance of gamma-cyclodextrin in humans. Food Addit Contam 16 (1999), 313-7 OLIVIER P, VERWAERDE F, HEDGES AR: Subchronic toxicity of orally administered Beta-Cyclodextrin in rats. J. American Coll. Tox., 10 (1991) 407-419 SEBESTYÉN G: The acute LD50 values of beta-cyclodextrin in CFY rats, CFLP mice and mongrel dogs. Report of Chinoin Pharmaceutical and Chemical Works (1980) SMITH TG, COX RA, BUIST DP, CROOK D, HADLEY JC, GOPINATH C: Beta-cyclodextrin toxicity to dogs by repeated dietary administration for 13 weeks. Preliminary study. Unpublished report No. ROQ 2/911089 of Huntingdon Research Centre Ltd.	

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	(1992) Van DOKKUM W, Van der BEEK EJ: Tolerance of ß-cyclodextrin in man. Unpublished report No. V 90.419 of TNO (1990), to AVEBE, Foxhol, The Netherlands	
5	**Context: Giving information in the package leaflet** Cyclodextrins are currently not included in the European Commission Guideline on excipients in the label and package leaflet of medicinal products for human. In the attached document, it is mentioned that: - The oral availability of cyclodextrins is very low - High doses may cause reversible diarrhea and cecal enlargement in animals - Cyclodextrins may influence the permeability of tissues and therefore the bioavailability of active substances given typically - Cyclodextrins can cause nephrotoxic effects in animals at high systemic exposure. Up to now, there is no proof of these effects in humans; however, data in children less than 2 years old are scarce. According to this document, the presence of cyclodextrins should be stated as a precaution (zero thresholds), because of limited information and possible interaction with active substances. ------- This draft can be confusing to companies that must comply with its requirements, and consumers who see warning labels on cyclodextrins and	In agreement with the comments, the text in the Q&A has been changed. The cited information is in agreement with the Background review for cyclodextrins.

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	wonder why. Different strong data have shown that HPBCD (for example) is a useful solubilizing and stabilizing agent for a wide variety of poorly water-soluble drugs. Information to date indicates that HPBCD does not induce vacuolization in the kidney nor nephrotoxicity at doses of 200 mg/Kg in rats or monkeys when given repeatedly over periods of 14 to 90 days. In addition, doses as high as 10 g/Kg were not acutely toxic in monkeys when given intravenously, nor in mice when given intra-peritoneally. It is possible that some osmotic effects may be generated by this non-electrolyte at high doses. HPBCD is not active in various mutagenicity tests, and is not causing lesion to red blood cells at relatively high doses when given intravenously. A number of clinical studies are reported in the literature and have shown that HP-BCD was well tolerated and safe in the majority of patients receiving HP-BCD at daily oral doses of 4–8 g for at least 2 weeks *(Irie and Uekama, 1997).* Higher oral daily doses of 16–24 g when given for 14 days to volunteers, resulted in increased incidences of soft stools and diarrhea. Therefore, based on these clinical data, HP-b-CD was considered to be non-toxic (at least for 14 days) if the daily dose is <16 g. In an intravenous dosing study *(Seiller et al., 1990)* single doses up to 3 g were found to have no measurable effect on kidney function and were well-tolerated by all volunteers. Following a 1 week intravenous study at a single dose level of 1 g, no adverse effects were reported *(Janssen Technical Bulletin, 1992).* The toxicity of alpha-cyclodextrin was examined in standard *in vitro* and *in*	

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	vivo toxicity tests. *Ames* tests and a micronucleus test demonstrate that alpha-cyclodextrin is not genotoxic. In acute toxicity tests with parenteral administration, the LD50 of alpha-cyclodextrin varied between 500- 1000 mg/kg bw (depending upon species and route of administration). In two 13-week oral toxicity tests, rats and dogs received alpha-cyclodextrin with the diet at concentrations of up to 20%. A few mild, physiological effects (including cecal enlargement, transient diarrhea or stool softening) were consequences of the indigestibility and microbial, intestinal fermentation of alpha-cyclodextrin. Alpha-cyclodextrin is not digested to absorbable glucose in the small intestine to any significant extent, but it is fermented by the colonic microflora like many other low-digestible carbohydrates. Therefore, alpha-cyclodextrin, has the nutritional properties of a fermentable dietary fiber, similar to so-called “resistant starch”. In animal studies, alpha-cyclodextrin was found to increase fecal bulk and to lead to stool softening if fed at high dietary concentrations. In humans, alpha-cyclodextrin attenuated the glycemic response to co-ingested starch, an effect that has been observed also with other dietary fibers such as beta-glucan or guar *gum* (Diamantis & B&, 2002; Diamantis et al., 2004). With regards to these physiological functions, alpha-cyclodextrin has the properties of a dietary fiber. In addition, the results of four experiments conducted in rats provide a coherent picture of the absorption, distribution, metabolism and excretion of alpha-cyclodextrin (van Ommen & de Bie, 1995 as cited in WHO, 2002; van Ommen et al., 2004).	

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	Taking into account the information concerning side effects associated with the use of cyclodextrins, history of safe use, would you agree to reconsider your labeling strategy?	
6	The Medicines Evaluation Board in the Netherlands considers that it should be clear from the revised Guideline on the "Excipients in the label and package leaflet of medicinal products for human use" and its related Questions and Answers that the guideline/Q&As is only intended to provide information to stakeholders on excipients with a relevant safety concern in cases where the acceptability of the excipient in the proposed quantity/concentration has been adequately justified by the company in the MA-dossier i.e. has been found acceptable by the regulatory authorities in view of an overall benefit to risk evaluation of the medicinal product and adequate pharmaceutical development. In order to clearly inform the readers of the guideline/Q&As on this important aspect, this statement should be included at the top of the guideline/Q&As. It is noted that this statement particularly applies to paediatric medicines.	This is a general issue, especially for the Guideline of excipients itself, and not just for the cyclodextrins. Therefore, from the cyclodextrin point of view, no comments.
6	It is not clear whether the Q&A will be a stand-alone document or should be read in addition to the current Guideline. In case the Q&A is intended to be a stand-alone document, an explanatory note to clarify the structure of the Table in Section 6 should be included. If it is to be read in conjunction with the current Guideline, this should be clearly mentioned.	This is also a general issue, and not CD related. No comments.
6	The purpose of the last column of the Table included in Section 6 "Comments (for health care professionals)" is not clear. In our opinion the information given in this column is in several cases relevant for health care professionals, and hence reference to include this information in the SmPC should be included. Furthermore, inclusion of information which is considered relevant for health care providers in the SmPC seems logical. One cannot expect health care professionals to read a Q&A document for	Again a general issue, not CD related.

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	additional clarification. It is suggested to replace the last column by two other columns; one for information to be included in the SmPC and a second column for additional comments for the benefit of applicants and competent authorities.	
6	In the title of this document and in the title of the guideline is mentioned '...Excipients in the label and package leaflet...'. However also advice regarding the information to be included in the SmPC is given. Therefore, we propose to change "in the label and package leaflet" into 'in the product information'.	A general issue. This document is only concerning cyclodextrin issues.
7	On November 20, 2014 EMA has published a "Background review for cyclodextrins used as excipients" (http://www.ema.europa.eu/docs/en_GB/document_library/Report/2014/12/WC500177936.pdf) Comments could be submitted until February 2015 (http://www.ema.europa.eu/docs/en GB/document library/Scientific guideline/2014/12/WC500177944.pdf). Comments which were submitted within the deadline by AESGP, the Association of the European Self-Medication Industry, are accessible on EMA's website (see attachment). Only shortly after the deadline we became aware of EMA's proposal for information in the package leaflet of medicinal products containing cyclodextrins (see Section 4.2 of "Background review for cyclodextrins used as excipients"). According to this proposal, the package leaflet of orally administered medicinal products containing alpha-cyclodextrin or gamma-cyclodextrin would have to inform the consumers that the cyclodextrin contained in this	Although alpha- and gamma-cyclodextrin are authorized as novel foods, there are still limits for safely intake (EFSA). However, the Q&A has been amended (see also above).

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	medicine - may alter the effects of other medicines, and - may cause intestinal disorders like diarrhea. The information for health care professionals would include an additional statement according to which - cyclodextrins can cause reversible diarrhea and cecal enlargement in animals at high doses (>1 g/kg bw/d) . These proposed labelling requirements conflict with the authorisations of alpha- and gamma-cyclodextrin as novel foods for which, in view of all available safety data and other pertinent information, no limits of use and no special labelling requirements have been laid down (Commission Decision 2008/413/EC and Commission Implementing Decision 2012/288/EU, respectively). Therefore, EMA's proposed information statements have the potential to confuse the consumers about the safety and tolerance of ingested alpha-cyclodextrin and gamma-cyclodextrin. These aspects have been duely examined when the safety of these two carbohydrates as novel foods have been examined. In the case of gamma-cyclodextrin, the food safety expert groups of Member States arrived jointly at the conclusion that gamma-cyclodextrine may safely be placed on the market as a novel food ingredient. In the case of alpha-cyclodextrin, the authorisation as novel food was based on a favourable EFSA Opinion. In either case, the aspects of intestinal tolerance and of interaction with other nutrients (e.g. vitamins) have duely been considered and addressed. Therefore, I should like to ask you to bring our concern about the	

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	conflicting EMA proposal to the attention of this Agency and to request a more differentiated approach for the labelling of the "natural", i.e. chemically not modified alpha- and gamma-cyclodextrin which are authorised novel foods on the one hand, and chemically modified cyclodextrins which do not have food status but which may play a useful role as excipients in certain medicinal products on the other hand. From a metabolic point of view, EMA should take into account that alpha-cyclodextrin is metabolized like any other non-digestible carbohydrate, i.e. dietary fiber, while gamma-cyclodextrin is subject to digestion by amylase and hence metabolized like amylose (starch). Chemically modified cyclodextrins, however, may not be digested as easily and may, therefore, have a different intestinal tolerance. Should EMA wish to examine any of the reports which have been relevant for the safety assessment of alpha- and gamma-cyclodextrin, we would be more than happy to provide this information to the Agency and thereby establish a direct contact.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
49-55	6	**Comment:** The document mainly deals with the safety of free cyclodextrin and not with the influences of cyclodextrin on the exposure of drugs. This may especially important if the complex of cyclodextrin and drug is administered parentally. In paragraph "What are cyclodextrins and why are they used as excipients?" should be mentioned that cyclodextrin can lower the free concentration of the drug and therefore the pharmacokinetics/pharmacodynamics will be changed significantly.	This is agreed, and the text has been changed accordingly.
52-53	6	**Comment:** Here drug-drug interaction is mentioned without specification. As drug-cyclodextrin complexes are considered not to be absorbed, here probably is meant "pre-systemic drug-drug interaction. **Proposed change:** Please add: pre-systemic drug - drug interaction".	This is agreed, and the text has been changed accordingly.
74	2	**Comment:** *"Cyclodextrins are absorbed poorly via mucosal membranes, but at high doses…"* **Proposed change:**	Because it depends on the type of CD, the product and the circumstances, so it is too variable to indicate a specific dose. Reading the whole document, one will become an idea of high and low doses.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		It is suggested to specify what is consider being a high dose.	
98-99	2	**Comment:** "*Alpha-CD, β-CD and RM-β-CD showed renal toxicity at relatively low doses after parenteral administration and thus seem not very suitable for medicinal products given intravenously*." This statement is vague, it would be preferable to provide a definitive comment as to whether the use of these excipients in parenteral products is acceptable. **Proposed change:** If the use of these excipients is acceptable the following change is proposed: "*Alpha-CD, β-CD and RM-β-CD showed renal toxicity at relatively low doses after parenteral administration* "	Whether these CDs are acceptable depends on the risk/benefit ratio of the product. Therefore, we suggest: "*Alpha-CD, β-CD and RM-β-CD showed renal toxicity at relatively low doses after parenteral administration,* ***and therefore rarely used in medicinal products given intravenously."***
108-111	2	**Comment:** "*Because of their lower renal function, children less than 2 years old may theoretically be less vulnerable to renal toxicity. However, a few cases on the use of intravenous products with high doses of HP-β-CD and SBE-β-CD in neonates and young children have been reported without signs of toxicity.*" **Proposed change:** Proposed change intended to increase clarity of this sentence. " *Children less than 2 years old may theoretically be less vulnerable to renal toxicity due to their lower baseline glomerular*	This is agreed and amended accordingly.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		filtration rate. *Data related to the use of cyclodextrins in very young children is limited. However, in a few cases reports, use of intravenous products with high doses of HP-β-CD and SBE-β-CD in neonates and young children did not result in signs of toxicity.*"	
108-111	6	**Comment:** Lines 108-111 seem to indicate that there may be no concerns with the use of cyclodextrins in children below 2 years of age based on theoretical grounds and literature reports. However, this is not in line with the proposed comment for health care professionals, stating 'In children less than 2 years, the lower glomerular function may protect against renal toxicity, but can lead to higher blood levels of cyclodextrins which may lead to extra-renal effects'. This indicates that there are some concerns on a theoretical basis. These should then also be added to lines 108-111. **Proposed change:** Because of their lower renal function, children less than 2 years old may theoretically be less vulnerable to renal toxicity but this can lead to higher blood levels of cyclodextrins which may lead to extra-renal effects. However, a few cases on the use of intravenous products with high doses of HP-β-CD and SBE-β-CD in neonates and young children have been reported without signs of toxicity [11,12,7].	This is agreed, and amended accordingly in combination with above.
116	2	**Comment:**	This is agreed and amended accordingly. However, a range is given (> 200–1000 mg/kg/day), because an exact number is

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		"*Although the oral availability of cyclodextrins is very low, high doses…"* **Proposed change:** It suggested to specify 'high doses' *"…high doses (> 1000 mg/kg/day)*"	not possible. It is just an indication.
120	2	**Comment:** "*Cyclodextrins can cause nephrotoxic effects in animals at high systemic exposure*." **Proposed change:** Proposed change intended to increase clarity of this sentence. "Some *cyclodextrins (alpha-cyclodextrins and beta -cyclodextrins) can cause nephrotoxic effects in animals at high systemic exposure. In contrast, derivatives of β-cyclodextrin (hydroxypropyl-β-cyclodextrin or sulfobutylether-β-cyclodextrin) or γ-cyclodextrin are not associated with adverse effects on kidneys or on renal function of animals.*"	This is agreed and amended accordingly. However, instead of "not associated" a more cautious "less associated" is used, because also the derivatives can show toxicity in animals.
125	1	**Comment:** Proposal to add text. **Proposed change:** We suggest to add the following text: *In several papers related to some drugs (i.e. NSAIDs), when them are linked with beta-cyclodextrines, there is frequently a claim for a better bioavailability, a faster onset of effect, and a better GI tolerability.*	This suggestion sounds a bit contradictory to what is known about CDs (e.g. Brewster and Loftsson, 2007), and would also be very product dependent. This suggestion is insufficiently founded, and therefore not suitable for section 5 of the Q&A. *Brewster, M. E., Loftsson, T., 'Cyclodextrins as pharmaceutical solubilizers', Advanced Drug Delivery Reviews*

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		For this last claim, however, no experimental data are provided.	*59, 2007, p. 645–666.*
128	2	**Comment:** All routes of administration: Comments (for health care professionals: "*Low doses of cyclodextrins are not expected to cause adverse effects. However, there is insufficient information on children less than 2 years*." **Proposed change:** It is suggested to specify in the text what is considered to be a low dose, as is indicated when referring to 'high dose'.	An indication for a low dose is considered to be < 20 mg/kg/day.
128	3	**Comment:** Oral administration of parent Cyclodextrins (alpha-, beta-, gamma-CD) ""Low doses of cyclodextrins are not expected to cause adverse effects. …": Considering the low absorption and the toxicological data, the suggested threshold of "zero" to trigger labelling, including quantitative information and safety statements in the package leaflet is not appropriate. The EMA document "Background review for cyclodextrins used as excipients" refers to the total daily oral doses of CDs when used as dietary supplements: "As dietary supplement the total daily oral dose of alpha-CD may reach 6000 mg/day, for beta-CD 500 mg/day and for gamma-CD 10 000 mg/day…". These daily doses are equivalent to the calculated oral PDEs in tables 2 and 4 of the	Not accepted. Because the effects of CDs are product related, it is very questionable to use such specific thresholds. See also the comments above.

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		EMA document and the suggested thresholds above which adverse effects may occur. In case of beta-CD, the 48-fold dose (24 g/day) was tolerated without adverse effects (see above). Although the calculated PDEs probably are large overestimations of risk, - as a precautionary measure - the daily doses calculated from oral PDEs in tables 2 and 4 of the EMA document should be adopted as thresholds for labelling and safety statements in the package leaflet/SPC of pharmaceutical products containing parent cyclodextrins. **Proposed change:** It is recommended to replace the threshold "zero" by 6000 mg/day for alpha-CD, 500 mg/day for beta-CD and 10 000 mg/day for gamma-CD (total daily oral doses in agreement with the calculated PDEs) and to provide quantitative information and safety statements in the package leaflet and SPC only when the medicinal product is intended for chronic use.	
128	2	**Comment:** All routes of administration: Information for the package leaflet: "*Talk to your doctor or pharmacist before giving this medicine to your child if (s)he is less than 2 years as the cyclodextrin contained in this medicine might cause undesirable effects*." **Proposed change:** This sentence should only be included for medicines with a paediatric indication, therefore the following is proposed:	This text has been changed into "Do not use in children < 2 years old unless recommended by your doctor." But the zero threshold is changed into 20 mg/kg/day. See also above.

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		"Talk to your doctor or pharmacist before giving this medicine to your child if (s)he is less than 2 years as the cyclodextrin contained in this medicine might cause undesirable effects [to be included only for medicines with a paediatric indication]."	
128	2	**Comment:** All routes of administration: Information for the package leaflet: **Proposed change:** Minor rewording in order to increase patient readability. "*The amount of cyclodextrin in each <volume/unit> is xx mg.* *Talk to your doctor or pharmacist before giving this medicine to your child if they are less than 2 years old as because the cyclodextrin contained in this medicine might cause undesirable side effects. The presence of cyclodextrin in this medicine may alter the effects of other medicines."*	This text has been changed into "Do not use in children < 2 years old unless recommended by your doctor." But the zero threshold is changed into 20 mg/kg/day. See also above.
128	2	**Comment:** All routes of administration: Information for the package leaflet: *"The presence of cyclodextrin in this medicine may alter the effects of other medicines."* In the main body of the guidance (lines 118 and 119) it is noted that, depending on their amount, cyclodextrins may influence the permeability of tissues and therefore the bioavailability of active substances given topically (nasal, rectal, dermal, ocular)." It is not clear why the statement included in the table (line 128)	This text has been removed, because it is not clear and useful information for the package leaflet. Effects are product specific and the safety aspects of CDs should have been considered during the development and safety assessment of the drug product, and should be clearly stated in the SmPC.

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		should apply to all routes of administration, and it is therefore suggested this should only be applied to routes of administration where there is evidence that permeability of tissues may be influenced (e.g. nasal, rectal, dermal, ocular).	
128	3	**Comment:** Oral administration of parent Cyclodextrins (alpha-, beta-, gamma-CD): “The presence of cyclodextrin in this medicine may alter the effects of other medicines” (PIL) and “The interactions of cyclodextrin should be stated and documented in the SmPC section 4.5“ Although used as excipients in a multitude of different drug formulations, no suspicion of adverse interactions have raised until now. In contrary, one feature of CDs is their demonstrated ability to mitigate toxicities of drugs (Hanumegowda et al. 2014). Furthermore, CD entrapment of drugs at the molecular level prevents their direct contact with biological membranes and thus reduces their side effects (by decreasing drug entry into the cells of nontargeted tissues) and local irritation with no drastic loss of therapeutic benefits (Challa et al. 2005). Interactions of ingested parent cyclodextrins with the absorption of fat-soluble vitamins or other lipophilic nutrients is not to be expected because the formation of inclusion complexes is a reversible process, gamma-CD is readily digested in the small intestine, and studies with the poorly digestible alpha-CD and beta-CD have shown that the	Partly accepted. Effects of CDs are product specific and the safety aspects of CDs should have been considered during the development and safety assessment of the drug product, and should be clearly stated in the SmPC, when relevant.

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		bioavailability of vitamins (A, D, and E) is not impaired (Background review for cyclodextrins used as excipients, EMA 2013). In the 'Background review' it is summarised: "… since there are no data where cyclodextrins increase the toxic effects of active substances, the estimated NOAELs … are considered reasonable, with or without active substances." The proposed statements on the possibility of unspecified interactions with active substances contradict the intention of SPC/PIL, because they do not provide relevant information for prescribers and patients that would lead to targeted measures. **Proposed change:** Statements on the possibility of interactions should not be included in the package leaflet and SPC of orally applied medicinal products containing parent cyclodextrins.	
128	3	**Comment:** **Oral administration of parent Cyclodextrins (alpha-, beta-, gamma-CD):** "May cause intestinal disorders like diarrhea" and comment for HCPs: "At high dose (> 1000 mg/kg/day) cyclodextrins can cause reversible diarrhoea and cecal enlargement in animals". The main side effects of oral administration of high doses of CDs to rats and dogs include flatulence and soft stools and are similar	Not accepted. The oral administration of HP-β-CD at daily doses of 16-24 g for 14 days to human volunteers, resulted in an increased incidence of soft stools and diarrhea (Irie T., Uekama K. (1997) Pharmaceutical applications of cyclodextrins. III. Toxicological issues and safety evaluation. J Pharm Sci. 86(2):147-62.)

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		to those related to poorly digestible carbohydrates and other osmotically active nutrients. These effects are reversible on withdrawal of treatment (Stella and He 2008). In a well-conducted short-term toxicity study in rats, no other effects of toxicological significance were observed (Olivier et al. 1991). Several studies in humans confirm confirm that parent CDs are tolerated without adverse effects up to doses which are far from the contents of CDs in medicinal products. It has to be stated that lower doses of oral administered parent CDs – that could be achieved by the intake of pharmaceuticals – do not induce any gastrointestinal symptoms, because the human gastrointestinal tract is physiologically capable of dealing with poorly digestible carbohydrates to a certain extent. None of the pharmaceutical products on the market contains high doses of > 1000 mg/kg/day, correspondent to more than 50 g of CDs. Not even massive overdose of medicinal products can result in comparable quantities of CDs. Therefore, the statement in the 'Background review' (4. Recommendations for the guideline, EMA 2013), that high doses may cause reversible diarrhea and cecal enlargement in animals, is correct, but it is not reasonable to draw the conclusion "…and therefore also in humans to some minimum extent". Moreover, the proposed wordings for prescribers ("Low doses of cyclodextrins are not expected to cause adverse effects" as well as "high doses of > 1000 mg/kg/day can cause reversible diarrhea and cecal enlargement in animals"), or patients ("may cause intestinal disorders like diarrhea", i.e. not dose-dependent adverse	

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		effect) are contradictory. **Proposed change:** As the "relevance to humans is minimal" (Background review for cyclodextrins used as excipients, 2.1 Oral products, EMA 2013), the proposed text for PIL and SPC should be deleted, because it does not provide relevant information for prescribers and patients.	
128	4	**Comment:** The two statements in Table 6 *"The presence of cyclodextrin in this medicine may alter the effects of other medicines"* and *"The interactions of cyclodextrin should be stated and documented in the SmPC section 4.5)"* are not applicable to the parenteral route of administration, but may be applicable to other routes of administration. The two statements should be deleted for the parenteral route of administration. Since the absorption phase is not involved when cyclodextrin is administered via the parenteral route, it is unlikely that cyclodextrin would alert the effect of other medicines. In addition, there are no data or literature to support the statement "the presence of cyclodextrin in this medicine may alter the effects of other medicines", when cyclodextrin is administered via the parenteral route. Therefore, it is also not clear what interaction data would need to be included in the SmPC section 4.5, for cyclodextrin administered via the parenteral route.	It is agreed that insufficient data are present for the possible interactions of parenteral cyclodextrin products. But theoretically all kinds of interactions are possible, also effects on kinetics. It is product specific, and should be dealt with per product. Anyhow, the statement "The presence of cyclodextrin in this medicine may alter the effects of other medicines" has been removed from the Information for the Package Leaflet column.
128	2	**Comment:**	It is agreed that the wording is not very specific, however the extra-renal adverse effects are theoretical, and there are not

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		Parenteral: Comments (for health care professionals): "*In children less than 2 years, the lower glomerular function may protect against renal toxicity, but can lead to higher blood levels of cyclodextrins which may lead to extra-renal adverse effects*." **Proposed change:** Please clarify what 'extra-renal adverse effects' are known to occur in young children with high blood levels of cyclodextrins and consider providing guidance to the health care professional regarding these effects. EFPIA is not familiar with published reports of extra-renal toxicity being observed in young children treated with drug formulations containing cyclodextrins.	enough data on young children to declare CDs totally safe. So as long as there are not sufficient data, it is recommended to take this theoretical possibility into mind.