24 September 2015
EMA/CHMP/SWP/684886/2013
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on the 'Guideline on the use of phthalates as excipients in human medicinal products' (EMA/CHMP/SWP/362974/2012)

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

Stakeholder no.	Name of organisation or individual
1	Association of the European Self-Medication Industry (AESGP)
2	Boehringer Ingelheim
3	Colorcon Limited
4	Dexcel Ltd.
5	Health Care Without Harm Europe
6	International Pharmaceutical Excipients Council of the Americas (IPEC-Americas)
7	Medicines Evaluation Board (MEB) in The Netherlands
8	Nordmark Arzneimittel GmbH & Co. KG, 25436 Uetersen, Germany
9	Sanofi
10	SciencePharma (Poland)
11	Xiphora Biopharma Consulting; David J Snodin
12	Bundesverband der Pharmazeutischen Industrie e. V. (BPI)

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	AESGP welcomes the opportunity of being consulted on this draft EMA guideline on the use of phthalates as excipients in human medicinal products.	N/A
2	General comment: Line numbers 257 to 259 (Implementation of new PDEs for existing authorised medicinal products) Are justifications to EMA or reformulations of a given product currently containing phthalates, still expected to be provided or done when the given product's phthalate limits are within the prescribed limits as per the guideline? For products with phthalates exceeding the limit and/or reformulations is not possible – discussions are expected with EMA on a case by case basis for acceptance. What is the proposal from EMA if following these discussions, this is not acceptable? Voluntary withdrawal? Phase-out of supplies? Timeline to get this done? If proposal is acceptable, label update alone is needed?	PDEs were established for DBP and DEP but not for PVAP, HPMCP and CAP. Products containing DBP and DEP at levels leading to exposures below the PDE will not require reformulation or a justification to the relevant competent authorities. The guideline states that the presence of DBP or DEP at levels giving rise to daily exposures above the PDEs could be accepted as exceptions, on a case-by-case basis taking into consideration the intended patient population, the disease seriousness and the presence or not of alternative treatment options. For instance, in severe or terminal disease conditions and its strict application is not considered

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		necessary for products where the risk of reproductive and developmental toxicity is outweighed by the benefits of treatment for patients. In such cases the potential risk of the presence of DBP or DEP above the PDE should be reflected in sections 4.6 and 5.3 of the Summary of Products Characteristics. Due to the absence of sufficient clinical evidence on phthalate-induced adverse effects in humans changes to the information in the label and package are not considered necessary. A time limit of 3 years (after coming into force of the final guideline) for the implementation of formulation changes and consequential regulatory applications, as necessary.
3	Colorcon is concerned with the recent EMA determination that the PDE for Polyvinyl Acetate Phthalate (PVAP) is limited to 2 mg/kg/day as we are aware that currently marketed products, such as Sodium Valproate formulations used to treat Epilepsy in the EU already exceed the proposed maximum exposure level.	The results of the new developmental toxicity study by Schoneker et al 2012 showed an absence of embryofetal effects at doses

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	Colorcon recently sponsored several studies, all consistent with current Good Laboratory Practice (GLP) and internationally recognized guidelines, to provide additional safety data to support current and new applications for polyvinyl acetate phthalate (PVAP) and PVAP co-processed with titanium dioxide (PVAP-T). The new PVAP studies included a 90-day sub-chronic dietary study in rats, a developmental toxicity study in rats and two genotoxicity tests. The new studies provide additional safety information to support the use of PVAP as a film coating polymer, matrix polymer and drug solubility enhancement agent in oral solid dosage forms for pharmaceutical applications. In addition, an acute oral toxicity study and a bacterial mutation test was conducted with PVAP-T. A copy of the study reports are included in a CD provided to EMA under in confidence. The study results are summarized below. The results of the new studies should be used to determine the Permitted Daily Exposure (PDE) for PVAP. PVAP and PVAP-T have a long history of safe use in drug products in many countries and are used commercially in Colorcon formulated products. <u>Acute Oral Toxicity Study</u> The acute oral toxicity of polyvinyl acetate phthalate (PVAP) was assessed in male and female rats that received PVAP by gavage at the maximum (limit) dose. Under the conditions of the study, the acute oral LD50 of PVAP was estimated to be greater than 5000 mg/kg in the rat. <u>90-day Sub-Chronic Dietary Study</u> The purpose of this study was to evaluate the potential toxicity and toxicokinetics of polyvinyl acetate phthalate (PVAP) when administered in the diet to Sprague Dawley CRL: CD (SD) rats (20/sex/group) at a dietary concentration of 0.75%, 1.5% and 5.0% for a	exceeding the doses associated with teratogenic effects in the developmental rat study reported by Schoneker et al 2003. This combined with uncertainties on the reliability of the data presented in Schoneker et al 2003 due to the poor reporting of the study findings resulted in the removal of the provisional PDE for PVAP. Therefore a PDE for PVAP was not adopted in the finalised guideline.

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	minimum of 90 days. Control animals (20/sex) received untreated standard laboratory diet. The following parameters were evaluated in this study: clinical signs, body weights, body weight changes, food consumption, test article consumption, ophthalmology, full functional observational battery assessments, clinical pathology parameters (hematology, coagulation, clinical chemistry, and urinalysis), gross necropsy findings, organ weights, and histopathologic examinations. All but two animals survived until scheduled sacrifice: one 0%-treated male was euthanized moribund on Day 56 due to a fractured rostrum, and one 5%-treated female was euthanized moribund on Day 84 due to a fractured tibia and fibula. These deaths were accidental and were not considered to be treatment related. Soft stools were observed in 5%-treated males throughout the dosing period. There were no consistent, dose-related, statistically significant PVAP-related adverse effects on body weight, body weight changes, ophthalmic examinations, functional observational data, hematology parameters, coagulation parameters, clinical chemistry parameters, urinalysis parameters (macroscopic and microscopic), or absolute or relative organ weights. Statistically significant mean increases in food consumption of up to 15.9% and 10.2% were observed in 5%-treated males and females, respectively, compared to the controls, likely as a result of compensating for the dilution in calories from the incorporation of PVAP at 5% of the diet. The overall mean PVAP doses were 0.44, 0.87, and 3.12 g/kg/day for the 0.75%, 1.5%, and 5%-treated male animals, respectively, and 0.52, 1.03, and 3.64 g/kg/day for the 0.75%, 1.5%, and 5%-treated female animals, respectively. There were no toxicologically meaningful gross or microscopic changes noted. The toxicokinetic phase could not be completed because an analytical method could not be developed for PVAP in blood plasma. In conclusion, daily administration of polyvinyl acetate phthalate (PVAP) in the diet was well	

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	tolerated in male and female rats up to a concentration of 5%. No PVAP-related toxicity or mortality was observed. Based on these results, the no-observed-adverse-effect level (NOAEL) was the 5% dietary concentration, which corresponds to a dose of 3.12 g/kg/day for males and 3.64 g/kg/day for females. Developmental Toxicity Study of Dietary PVAP in Rats The purpose of this study was to assess the potential developmental toxicity of polyvinyl acetate phthalate (PVAP) in Crl: CD (SD) presumed-pregnant female rats (from implantation to closure of the hard palate). This study was consistent with ICH Harmonized Tripartite Guideline stages C and D of the reproductive process. One hundred presumed pregnant Crl: CD (SD) rats were randomly assigned to four exposure groups (Groups I through IV), 25 rats per group. Polyvinyl acetate phthalate (PVAP) was administered as a dietary admixture in Certified Rodent Diet® ((meal form) #5002, PMI® Nutrition International, St. Louis, MO, USA) at concentrations of 0, 0.76, 1.5, and 3.0% Female rats were given continual access to the formulated diets on days 6 through 20 of presumed gestation (DGs 6 through 20). All surviving rats were euthanized and Caesarean-sectioned on DG 21. The following parameters were evaluated: viability, clinical observations, body weights, feed consumption, necropsy observations, Caesarean-sectioning and litter observations, including gravid uterine weights, fetal body weights and sex, and fetal gross external, soft tissue and skeletal alterations. Mean daily doses were 567.0, 1139.1 and 2324.6 mg/kg/day in Groups II, III and IV, respectively, for the entire dosage period (gestation days 6 to 20). There was no test article-related mortality. One rat in the 0% exposure group was sacrificed due to a broken hind limb. All other rats survived to scheduled sacrifice. There were no test article related clinical or necropsy observations. Body weights, body weight gains, gravid uterine weights and absolute and relative feed consumption values were	

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	unaffected by concentrations of PVAP in the diet as high as 3%. No Caesarean-sectioning or litter parameters were affected by PVAP at levels in the diet as high as 3%. No gross external, soft tissue or skeletal fetal alterations (malformations or variations) were caused by PVAP at levels in the diet as high as 3%. Fetal ossification was comparable among the four groups (control and 3 PVAP-treated groups). In conclusion, there were no consistent, treatment-related, dose-dependent, statistically significant adverse effects on any of the maternal and fetal parameters evaluated. Therefore, the maternal and developmental no-observable-adverse-effect level (NOAEL) of PVAP is the highest concentration administered, 3.0% (equivalent to 2324.6 mg PVAP/kg/day). Genotoxicity Studies A Bacterial Mutation Test and a Chromosome Aberration Test were performed to evaluate the potential genotoxicity of PVAP. There was no evidence of genotoxic activity of PVAP in the *in vitro* Bacterial Mutation Test and no evidence of clastogenicity in the in vitro Chromosome Aberration Test for induction of chromosome damage. PVAP-T Toxicology Study Results Colorcon conducted two GLP studies to provide further supporting information for the safety of PVAP-T. An acute oral toxicity study and a genotoxicity test were conducted. The study results are summarized below. Acute Oral Toxicity Study The acute oral toxicity of co-processed Polyvinyl Acetate Phthalate and Titanium Dioxide (PVAP-T) was assessed when administered by gavage as a single oral dose to Sprague Dawley male and female rats. There were no deaths and no signs of intoxication. The acute oral LD_{50} of PVAP-T was estimated to be greater than 5000 mg/kg in the rat, the	

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	highest dose tested and the recommended limit dose. Genotoxicity Test A bacterial mutation test was performed to evaluate the potential genotoxicity of PVAP-T. PVAP-T did not show any evidence of genotoxic activity. It may be concluded that PVAP-T is not genotoxic. Analytical Studies to Bridge PVAP-T to the PVAP Studies The toxicological data for PVAP is used to support the safety of PVAP-T. In order to bridge PVAP-T to the PVAP data, Colorcon conducted several analytical studies to demonstrate that PVAP and Titanium Dioxide (TiO2) are not chemically altered during the manufacturing process or during transit through the gastrointestinal tract. PVAP-T is a co-processed excipient which is manufactured by combining PVAP and TiO2 using a physical process that results in an intimate mixture of the particles. No chemical modification occurs in the process. A series of studies were performed to determine if PVAP-T co-processed excipient exhibits the same chemical composition as would exist for a standard physical blend of PVAP and TiO2. Three batches of a physical blend of PVAP and TiO2 and co-processed PVAP-T were manufactured according to the standard operating procedures. The batches used the same lots of raw materials and were individually sampled and tested. Samples were evaluated using standard compendial release testing and other analytical techniques consisting of FTIR spectral analysis, size exclusion chromatography with photodiode array detection, reversed phase HPLC, differential scanning calorimetery, thermalgravemetric analysis, powder X-ray diffraction, particle size analysis both wet and dry, headspace gas chromatography, and bio-relevant dissolution testing. The results of this study clearly demonstrate that there were no chemical differences	

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	between a physical blend or co-processed PVAP and titanium dioxide. The routine QC testing met the predetermined specifications and did not show any trends or differences between the blended or co-processed materials. Testing was performed in USP gastric and intestinal fluid, both with and without enzymes, to evaluate the effects of co-processing on the PVAP polymer with titanium dioxide when exposed to different pH and enzymatic activities. No difference in UV/Vis spectra was observed between the co-processed and blended PVAP-T samples in the four media tested. PVAP was not soluble in either of the fluids. There is no chemical difference between the PVAP and TiO2 physical blends and the PVAP-T co-processed product. No signs of any degradation products were found in the PVAP-T samples. This information helps to bridge to the toxicology studies conducted with PVAP and supports the safety of PVAP-T. In conclusion, PVAP-T is essentially equivalent to PVAP and TiO2 since the chemical composition, physiochemical properties and specifications of the PVAP and TiO2 are unchanged during manufacture of PVAP-T. The toxicological/safety data that support the safety of PVAP can be used to support the safety of PVAP-T when used as an excipient. A copy of the study is included in the CD provided to EMA in confidence. **Independent Expert Safety Evaluation of PVAP and PVAP-T** The International Pharmaceutical Excipients Council (IPEC) of the Americas developed a New Excipient Safety Evaluation Procedure. The goal of this process is to provide an independent evaluation of the safety and regulatory acceptance of a new excipient before a regulatory filing. The process is meant to mirror that of regulatory agencies, ideally providing confidence to pharmaceutical manufacturers that the excipient will be acceptable in their formulations. This procedure has been discussed with the U.S. FDA and they acknowledged that this type of review would be very beneficial when evaluating a new	

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	excipient. The New Excipient Evaluation Committee (NEEC) is the expert panel that conducts the excipient safety evaluation. The NEEC Expert Panel independently and collectively critically evaluated the data and information summarized for PVAP and PVAP-T and concluded that PVAP and PVAP-T are safe for their intended use as an excipient in film coating formulations and matrix tablet drug products. Based on the toxicology study results, safety assessment and the estimated exposure assessment in the NEEC's report for PVAP and PVAP-T, the expert panel concluded that PVAP and PVAP-T could safely be used in drug products up to 829 mg per day. The complete NEEC report is included on the CD provided to EMA. **Summary and Conclusion** The series of safety studies conducted by Colorcon with PVAP include a definitive 90-day subchronic toxicity study, a developmental toxicity study and several genotoxicity tests. There were no adverse effects reported in the 90-day subchronic toxicity study and the developmental toxicity study. PVAP was not genotoxic. The no-observed-adverse-effect level (NOAEL) in the GLP 90-day subchronic study was the 5% dietary concentration, which corresponds to a dose of 3.12 g/kg/day for males and 3.64 g/kg/day for females, the highest level tested. The chemical composition, physiochemical properties and specifications of PVAP-T are unchanged during manufacturing process based on the analytical studies conducted by Colorcon. Therefore, the toxicological data that support the safety of PVAP can be used to support the use of PVAP-T as an excipient. Based on the toxicology study results, safety assessment and the estimated exposure assessment in the NEEC's report for PVAP and PVAP-T, the expert panel recommended that PVAP and PVAP-T could safely be used in drug products up to 829 mg per day (for further information see the NEEC report included on the CD). This recommended amount was	

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	based on a worst case exposure model and the safety data could potentially support higher levels of use if assessed. It is Colorcon's intent to publish these additional safety studies in the near future. **Nomenclature** There are concerns about low molecular weight phthalate materials such as di-butyl phthalate (DBP). The specific toxicity of this molecule is due to its metabolic conversion to their corresponding monoester. There has been confusion about the safety of two groups of materials, low molecular weight phthalates and high molecular weight polymeric phthalates. The safety of these two groups should be independently assessed. It is our opinion, since both of these groups are included in this guidance, that there should be a clear distinction made between them. It is inappropriate to identify large molecular weight polymers such as PVAP and imply that they have similar concerns simply based on the fact that they have the word phthalate in their name. In fact, PVAP is simply a polymeric polyvinyl acetate backbone with ester linkages formed between the hydroxyl groups and a phthalate group. These molecules are extremely large and are very different than the short chain alcohols that are used to produce DBP. We request that EMA provide an explanation in the guidance document explaining the differences between the low molecular weight materials such as DBP and high molecular weight enteric polymers such as PVAP.	
4	<u>We would like to clarify the following issue:</u> The concerned "Guideline on the use of phthalates as excipients in human medicinal products" relates to "hydroxypropyl methylcellulose acetate phthalate (HPMCP)".	• The nomenclature of Hydroxypropylmethylcellulose phthalate (HPMCP) was corrected.

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	We would like to draw your attention to the fact that the material “hydroxypropyl methylcellulose acetate phthalate” is related to as HPMCAP, as opposed to HPMCP which is Hydroxypropyl methyl cellulose phthalate. Regarding HPMCP, according to the mentioned guideline (section 6.5) and the “handbook of Pharmaceutical Excipients (fourth edition)”, studies concerning its toxicity have shown no evidence of safety concerns. Furthermore, it was noted that the guidance for Industry “limiting the use of specific phthalates as excipients (Food and Drug Administration December 2012)” applies only to DBP and DEHP and does not include either hypromellose phthalate (HMP), cellulose acetate phthalate (CAP), or polyvinyl acetate phthalate (PVAP). According to the article*, the term “phthalate” has been defined by the U.S. Environmental Protection Agency (EPA) and other regulatory agencies to identify diesters of orthophthalic acid, also called simply phthalic acid, an aromatic dicarboxylic acid in which the two carboxylic acid groups are located on adjacent carbons (positions 1 and 2) in the benzene ring. Both di-*n*-butyl phthalate (DBP) and di-(2-ethylhexyl) phthalate (DEHP) are examples of such phthalates; these phthalates are chemically and toxicologically distinct from diesters of isophthalic or terephthalic acids, which are not considered to be true “phthalates,” as defined by the U.S. EPA (2012). HMP, PVAP, and CAP are polymers that have been modified by esterification with orthophthalic acid groups. These high-molecular-weight polymers differ markedly from the short-chain alcohols used to produce DEHP and DBP, and their chemical properties are very different. The toxicity associated with DBP and DEHP stems from their bioconversion to their respective monoesters; this bioconversion is unlikely for PVAP and not possible for HMP or CAP.	• A statement addressing the difference between (a) the low molecular ortho-phthalate esters (DBP and DEP) and (b) the high molecular weight phthalate polymers (CAP, HPMCP and PVAP), and the reasons the two groups of compounds were selected for review has been included in the finalised guideline.

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	We would like your clarification on the material this guideline relates to, any restriction it may apply to, and your rational for including the material in this guidance, based on the above. <u>We are especially interested in HPMCP (Hydroxypropyl Methylcellulose Phthalate) – a well known and widely used enteric coating in the pharmaceutical industry.</u> * Defining “Phthalates”, William Dale Carter, Environ Health Perspect. 2012 November; 120(11): a416. , Published online 2012 November 1	
5	Pharmaceutical excipients are essential components of drug products, but they are not inert substances and like all chemicals can have potential toxic effects. Several studies have suggested that medication can be an important source of exposure to phthalates[1–3]. And, a recent study identified more than 100 drugs that use phthalates as excipients in US[4]. However, the potential effects on human health of these exposures are mostly unknown. HCWH Europe believes the use of phthalates as excipients should be extremely limited. In particular, DBP (dibutyl phthalate) a chemical classified as toxic to reproduction, which may impair fertility and cause harm to unborn children, should be banned, as safer alternatives are available. Increased urinary concentrations of phthalate metabolites have been reported for individuals taking mesalamine, aminosalicylates, pancreatic enzyme products and other drugs products but further research and consideration of the contribution of medications to phthalate exposure is needed[1–3,5,6]. For example, among mesalamine users, the mean urinary concentration of monobutyl phthalate (MBP), the main DBP metabolite was 50 times higher than the mean of non-users[2,3]. Users of didanosine, omeprazole, and theophylline products, some of which may contain diethyl phthalate (DEP), had mean urinary concentrations of monoethyl phthalate, the main DEP metabolite, significantly higher than the mean for nonusers[2]. Exposure can vary according to manufacturer specific formulation characteristics, dosage form, dose, and date of use and country of manufacturer but this information is	The safety of the use of DBP in human medicinal products was evaluated and a PDE of 0.01 mg/kg body weight/day, based on reproductive effects in rats, was adopted. The available data supporting the relevance of phthalate induced reproductive toxicity/endocrine effects in humans is not conclusive therefore the removal of DBP as an excipient in human medicinal products was not recommended. However the very low PDE established for DBP will limit exposures in the patient population to a level that is not considered to be

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	most of the times lacking. Not allowing for an informed decision from the side of prescribers or patients. Inclusion of a specific phthalates as excipient is manufacturer specific and on occasions dosage form and strength specific. For different groups of medications, only one formulation contains phthalates, implying that there are both other formulations that use other alternative excipients[4,6]. If safer alternatives are available then these should be promoted and used. Phthalates are considered endocrine disrupting substances that unlike other chemicals can have effects at very low concentrations. Exposure to phthalates in humans has been related with developmental disorders, including testicular cancer, diminished sperm levels, insulin resistance leading to obesity and attention-deficit disorders[7]. Permitted Daily Exposures for individual phthalates or for individual products do not take in consideration their interaction and cumulative effects or the risks of ubiquitous presence of phthalates in personal care products, cosmetics, packaging material, medical devices, toys, etc.. In addition, for endocrine disrupting chemicals no thresholds of toxicity can be safely set. According to the substitution principle, harmful chemicals should always be substituted whenever safer alternatives are available. This is also the recommendation of CHMP article 5(3) - "any risk would be acceptable only on the condition that this excipient cannot be substituted with a safer available alternative". Therefore, the use of phthalates as excipients should be extremely limited. DBP, in particular, should not be allowed as an excipient in human medicines. The present draft guidance should also introduce clear indications of how these substitutions should be made in order to push the industry to move away from these compounds. Certain groups of the population, as pregnant women and children, are particularly vulnerable to phthalate exposure and this vulnerability needs to be considered in the guidelines. The safety data of excipients, similarly to active pharmaceutical ingredients, is in most instances based solely on adult exposures[89]. Performance, stability, drug bioavailability and safety in pediatric subpopulations are often unknown[10]. Neonates in particular can be	toxicologically significant based on currently available data.

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	considered very vulnerable due to the ongoing development and immaturity of their organs, including the small intestine where drugs are mostly absorbed[8]. The guidelines should also take in consideration therapeutic duration. Some patients groups are chronically exposed from repeated daily ingestions of medications containing phthalates and can because of these be at higher risk of exposure to phthalates. A pharmaceutical manufacturer should be prepared to demonstrate the safety of the excipients and of the proposed exposure to all to all age groups for the expected therapeutic duration. HCWH welcomes the initiative of the European Medicines Agency to incorporate product information of phthalate-containing medicinal products in the label and leaflet of products. This will allow prescribers and consumers to select alternative products that are phthalate free and should be introduced both for products in the market and new products. However, the exact amount of these substances in drug formulations should be also made available. Without quantitative information the estimation of precise exposure and assessment of harmfulness is not possible. The draft guidance recommends Permitted Daily Exposures values aimed at reducing the phthalate content of medicines but these recommendations are not strong enough. The European Medicines Agency should ban the use of DBP in excipients and should promote the substitution of other phthalates to help reduce the widespread exposure of the general population to phthalates, particularly in vulnerable groups as children and childbearing woman. 1. Hauser, R., Duty, S., Godfrey-Bailey, L. & Calafat, A. M. Medications as a Source of Human Exposure to Phthalates. *Environmental Health Perspectives* **112,** 751–753 (2004). 2. Hernández-Díaz, S., Mitchell, A. a, Kelley, K. E., Calafat, A. M. & Hauser, R. Medications as a potential source of exposure to phthalates in the U.S. population. *Environmental Health Perspectives* **117,** 185–9 (2009).	

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	3. Hernández-Díaz, S. *et al.* Medications as a potential source of exposure to phthalates among women of childbearing age. *Reproductive Toxicology* **37,** 1–5 (2013). 4. Kelley, K. E., Hernández-Díaz, S., Chaplin, E. L., Hauser, R. & Mitchell, A. a. Identification of phthalates in medications and dietary supplement formulations in the United States and Canada. *Environmental Health Perspectives* **120,** 379–84 (2012). 5. Keller, B. O., Davidson, a G. F. & Innis, S. M. Phthalate metabolites in urine of CF patients are associated with use of enteric-coated pancreatic enzymes. *Environmental Toxicology and Pharmacology* **27,** 424–7 (2009). 6. Nguyen, G. C. Phthalates in 5-Aminosalicylates: *Journal of Current Clinical Care* 14–21 (2012). 7. Wittassek, M., Koch, H. M., Angerer, J. & Brüning, T. Assessing exposure to phthalates - the human biomonitoring approach. *Molecular Nutrition & Food Research* **55,** 7–31 (2011). 8. Yochana, S., Yu, M., Alvi, M., Varenya, S. R. I. & Chatterjee, P. Pharmaceutical excipients and pediatric formulations. *Chemistry Today* **30,** 56–61 (2012). 9. Lass, J. *et al.* Hospitalised neonates in Estonia commonly receive potentially harmful excipients. *BMC Pediatrics* **12,** 136 (2012). 10. Tuleu, C. & Breitkreutz, J. Educational paper: formulation-related issues in pediatric clinical pharmacology. *European Journal of Pediatrics* **172,** 717–20 (2013).	
6	**The Facts about Phthalate Polymer Excipients** The International Pharmaceutical Excipients Council of the Americas (IPEC-Americas) represents companies who produce and use high quality pharmaceutical excipients. IPEC-	

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	Americas recently reviewed draft guidance, “Guideline on the use of phthalates as excipients in human medicinal products” (EMA/CHMP/SWP/362974/2012) and would like to clarify the terminology, and rectify any confusion caused by the colloquial use of the term “phthalate” in industry, academia, government, and by the general public. **Nomenclature** The term “phthalate” has been used by regulatory agencies to identify diesters of ortho-phthalic acid. Ortho-phthalic acid, otherwise known as phthalic acid, is an aromatic dicarboxylic acid with two carboxylic acid groups located on adjacent carbons (positions 1 and 2) in the benzene ring. Both di-n-butyl phthalate (DBP) and di-(2-ethylhexyl) phthalate (DEHP) are examples of ortho-phthalic acid diesters or phthalates, and are chemically and toxicologically distinct from diesters of iso- or tere-phthalic acids. Despite the fact that diesters of iso- and tere-phthalic acids are not considered true “phthalates”, they have been grouped together with ortho-phthalic acid diesters in the past by several publications through the colloquial use of the term “phthalates”. Application of the term phthalates to all forms of phthalic acid diesters and not just the ortho-phthalic acid diesters, has created unsubstantiated and erroneous safety concerns. The specific toxicological concern associated with DEHP and DBP arises from their metabolic conversion to their corresponding monoesters. **Uses of phthalate ester polymers in pharmaceutical formulation** Phthalate ester polymers are more soluble at a higher pH than at a low pH. This chemical property can be used to formulate pharmaceutical products that are designed to release the active drug in the gastro-intestinal (GI) tract after passing through the stomach, i.e. as enteric coating agents. In such applications the polymer coating is approximately 5 - 10%[1] of the tablet or capsule core weight. Phthalate ester polymers may also be used in the	

[1] Handbook of Pharmaceutical Excipients, 7th Ed, Rowe RC, Sheskey PJ, Cook WG and Fenton ME (eds.), Pharmaceutical Press, London and American Pharmacists Association, Washington, DC, (2012)

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	manufacture of modified release products, e.g. extended or prolonged release formulations. Depending on the mechanism of prolonging or extending the release of the drug, the amount of polymer in the final formulation may approach 30%. Recently, phthalate ester polymers have been used to help stabilize amorphous drugs through the preparation of spray-dried dispersions and hot melt extrusions of the drug and polymer. In such applications, in excess of 50% of the polymer-drug dispersion will be the polymer. However, the concentration of polymer in the final tablet will likely be lower because of the addition of other excipients to aid capsule filling or tablet compaction. **Stability of phthalate ester polymers** Phthalate ester polymers are stable when stored in a sealed container and away for extremes of temperature and humidity. However, like other esters, phthalate ester polymers are susceptible to degradation when subjected to conditions of high humidity and elevated temperature for an extended period of time. The degradation of the polymers results in the cleavage of ester linkages which then releases the free acid, such as phthalic acid or acetic acid depending on the polymer. This is a well-characterized phenomenon and the pharmacopeial monographs for the polymers have established limits for free acid levels. **Biopharmaceutics of phthalic acid** Phthalic acid released during the storage of drug products containing phthalate ester polymers has the potential to be absorbed from the GI tract following the oral ingestion of the drug product. However, because phthalic acid is a dicarboxylic acid that is highly polar and ionized at high intestinal pH (pk_{a1} 2.943; pk_{a2} 5.432)[2], the amount of phthalic acid absorbed from the GI tract is likely to be low. This is supported by available literature[3]	

[2] Albert A and Serjeant EP, The Determination of Ionization Constants, 2nd Ed., Chapman and Hall, London (1971)
[3] Williams DT and Blanchfield BJ, Retention, excretion and metabolism of phthalic acid administered orally to the rat, Bulletin of Environmental Contamination and Toxicology, (1974), **12** (1), 109 - 112.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	which states that, in the rat, most of orally administered phthalic acid was excreted in the feces, and that no detectable drug remained in the organs of the animals at 24 hr after dosing, thus indicating a relatively short elimination half-life ($t_{0.5}$). These authors also stated that the phthalic acid was not metabolized in the rat. In summary, the systemic exposure to free phthalic acid following oral administration is likely to be very low as it would be poorly absorbed from the GI tract. Thus the potential for systemic exposure of patients to free phthalic acid resulting from the degradation of phthalate ester polymers is very low. **Other Regulatory Guidance on Phthalate Excipients** In the March 2012 draft version of FDA's "Guidance for Industry - Limiting the Use of Certain Phthalates as Excipients in CDER-Regulated Products", it is recommended that the pharmaceutical industry avoid the use of two specific phthalates as excipients in CDER-regulated drug and biologic products: dibutyl phthalate (DBP) and di(2-ethylhexyl) phthalate (DEHP). On page 2, line 76 of the Draft Guidance document, the FDA is careful to note that the recommendations in the guidance apply only to DBP and DEHP. Nonetheless, suppliers of excipients have inquiries from customers as to the applicability of the guidance to unrelated products that include "phthalate" in their chemical name, an unfortunate consequence of chemical naming conventions and the use of the term "phthalate plasticizers" or simply "phthalates" to describe particular diesters of ortho-phthalic acid. This confusion is not limited to the marketplace, but is seen even in the scientific literature. As discussed above, there are chemical differences between various products that include "phthalate" in their name so that pharmaceutical manufacturers selecting excipients for use in their FDA-regulated products may distinguish between the class of molecules that is the subject of the Draft Guidance and those that are not. Currently ECHA restricts for classified phthalates including DEHP, DBP, BBP and DIBP. All aforementioned phthalates have been classified as reprotoxins and the main issue has been	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	use of some of these phthalates in plastics including children's toys and medical devices. There is no mention of C-A-P, HMP or PVAP in the current ECHA list of restricted phthalates. The term "phthalate" has been used by the EPA and other regulatory agencies to identify diesters of ortho-phthalic acid, also called simply phthalic acid, an aromatic dicarboxylic acid in which the two carboxylic acid groups are located on adjacent carbons (positions 1 and 2) of the phenyl ring of the molecule. Both DBP and DEHP are such phthalates. It is widely recognized that such phthalates are chemically and toxicologically distinct from diesters of iso- and tere-phthalic acids which are not considered to be "phthalates." **Introduction** Deleterious effects of stomach acid on a variety of orally-administered pharmaceutical products has been appreciated for decades. To preserve the integrity of these labile products in the acidic environment of the stomach, specific excipient materials have been developed to provide an enteric coating on the final formulated products. This enteric coating remains intact in acidic media, and dissolves in the relatively neutral environment of the intestines, where dissolution and absorption of the products occur. Some of the earliest materials to be developed for this purpose were polymers containing ortho-phthalic acid as a substituent, and many of these same materials continue to be used extensively today. During this time, other compounds containing short-chain alcohols esterified with ortho-phthalic had been developed for use as plasticizers, and recent data suggest that many of these phthalate plasticizers pose significant hazards to human health and the environment. Despite substantial differences in the chemical properties between the phthalate plasticizers and polymers containing ortho-phthalate acid, recent safety concerns for the phthalate plasticizers has prompted some scientists to question whether the polymers that are used as excipients for enteric coatings of pharmaceuticals pose similar safety concerns. Accordingly, this review serves to clarify the underlying physical/chemical properties of these excipients and to summarize the data which supports the continued safe usage of these materials.	

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	Cellulose Acetate Phthalate Cellulose acetate phthalate (C-A-P; CAS registry no. 9004-38-0) is a pH-sensitive cellulose derivative designed for coating pharmaceutical tablets or granules or as a matrix material in solid dose forms. Chemically, C-A-P is composed of a cellulose polymeric backbone, to which approximately 24% and 35% of the available hydroxyl substituents are esterified with acetate and o-phthalic acid moieties, respectively. In 1937, C-A-P was first described by Malm and Waring in U.S. patents no. 2,093,462 and 2,093,464 (Malm *et al.,* 1951). Since only one of the two carbonyl groups of the o-phthalate moieties is bound to the cellulose polymer, the other is available to form alkaline salts which are insoluble in media with a pH of about 5.8 or less, but are soluble when the pH of the medium is increased. For this reason, it was determined that C-A-P is a useful pharmaceutical excipient to create enteric-coated dosage forms, which remain intact in the highly acidic environment of the stomach, but dissolve upon entering the duodenum, due to the presence of bicarbonate-rich bile which causes the pH of the luminal contents to increase. Indeed, clinical evidence of these properties was obtained by Hodge et al in 1944 who used a radiographic technique to visualize the sites of release of barium sulfate from tablets or capsules that were uncoated or coated with C-A-P prior to ingestion by subjects. In these studies, it was determined that despite evidence that dissolution was occasionally observed to occur in the stomach, in the majority of subjects (between 79 and 100 per cent of trials), disintegration of the dosage form was determined to occur reliably in the gastro-intestinal tract in the 8 hours following ingestion (Hodge *et al.,* 1944). The use of C-A-P as an enteric coating material was first described in 1940, in U.S. patent on. 2,196,768 (Malm *et al.,* 1951), and an official monograph first appeared in the National Formulary XVI (1985). In 1998, the official name for C-A-P was changed to cellacefate NF, and most recently, a harmonized monograph for cellacefate NF was adopted in the second supplement to USP35/NF30, effective December 1, 2012, wherein Cellacefate NF, is defined as a reaction product of phthalic anhydride and a partial acetate ester of cellulose. It	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	contains not less than 21.5% and not more than 26.0% of acetyl (C_2H_3O) groups and not less than 30.0% and not more than 36.0% of phthalyl (*o*-carboxybenzoyl) ($C_8H_5O_3$) groups, calculated on the anhydrous, acid-free basis (United States Pharmacopeial Convention and USP 2011). In the early 1940's, as C-A-P was recognized as a potential excipient for pharmaceutical applications, the first chronic safety studies were conducted by Harold Hodge in 1944, in which groups of rats and dogs were fed C-A-P daily for a period of one year (Hodge, 1944). In the rat study, 4 groups of 20 rats each were fed diets containing 0, 5, 20, and 30 percent C-A-P daily for one year. The rats on high intakes of C-A-P showed a reduction in growth rate which increased with the dosage. On autopsy, the rats were in good condition and no abnormalities were observed except that the average stomach weight tended to increase with higher doses of C-A-P. From histological examinations, no consistent pathological changes were demonstrated. High doses of C-A-P in the diet tended to produce a mucilaginous character of the material in the intestinal lumen. From these observations it is concluded that the high levels of C-A-P in the diet of rats interfere quantitatively and mechanically with the absorption of food. No toxic action of C-A-P has been found in rats (Hodge, 1944). In the dog study, 3 groups of 2 dogs each were fed 1, 4, and 16 grams, respectively, of C-A-P during a period of one year. The dogs remained in excellent health and condition throughout the experiment and no consistent pathological changes were discovered at autopsy. There was no evidence of any toxic effects of C-A-P under these conditions, and from these studies, it was determined that in general C-A-P seems to be remarkably inert as a compound of the diet (Hodge, 1944). In 1996, the Safety Committee of IPEC-Americas issued proposed guidelines for the safety assessment of pharmaceutical excipients (Steinberg *et al.,* 1996). Using this approach, further studies were performed to assess the safety of C-A-P, consisting of subchronic and developmental toxicity studies in rats (Kotkoskie *et al.,* 1999), and a series of genotoxicity studies (Batt and Kotkoskie, 1999). In the subchronic studies, groups of Sprague-Dawley	

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	rats (20/sex/group) were fed diets that contained 0 (control), 5,000, 25,000, or 50,000 ppm of a commercial product (Aquateric®; FMC Corporation) that was 67.9% C-A-P, for a period of 90 days. No mortality, clinical signs or toxicity or adverse toxicological effects were observed in any treatment group, following evaluations of hematology, serum chemistry, body weights, feed consumption, ophthalmological examinations or histological evaluations of tissues (Kotkoskie *et al.,* 1999). In the developmental toxicity study, groups of pregnant Sprague-Dawley rats (25/group) were fed diets that contained 0 (control), 5,000, 25,000, or 50,000 ppm of Aquateric® on gestational days 6-15. No evidence of maternal toxicity or fetotoxicity or embryotoxicity was noted. Based upon the results of these studies, the no-observed-adverse-effect-level (NOAEL) for C-A-P was determined to be greater than 50,000 ppm of Aquateric®, which corresponds to a daily intake of approximately 3600 mg/kg (581 mg/kg Human Equivalent Dose; FDA, 2005). With an estimated daily intake of 4 mg/kg in humans, these data suggest that the margin of safety for Aquateric® is 145 (Kotkoskie *et al.* 1999). The margin of safety was calculated in accord with the FDA Pharm/Tox Guidance entitled "Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, July 2005. Genotoxicity studies also were performed in 1999 using Aquateric®, which contained 67.9% C-A-P. Tests included the Ames bacterial mutagenicity assay, the mouse lymphoma mammalian cell mutation assay, and the mouse micronucleus assay. In the Ames assay, Aquateric® was not mutagenic when tested in Salmonella typhimurium cell strains TA98, TA100, TA1535, TA1537, and TA1538, with or without metabolic activation. A mouse lymphoma assay was conducted using concentrations of Aquateric® that ranged from 116 to 2000 µg/mL or 116 to 1250 µg/mL in the absence or presence of metabolic activation, respectively. No increase in mutation frequency was observed at any concentration of Aquateric® tested. A mouse micronucleus assay was conducted using a single oral dose of 7200 mg/kg of Aquateric®, which represented a dose of C-A-P of 5000 mg/kg, and bone marrow was harvested at 24, 48, or 72 hours after treatment. The data indicated that there were no significant increases in the number of mouse bone marrow micronucleated	

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	polychromatic erythrocytes at any time following treatment with Aquateric®. These collective data indicate that C-A-P is not genotoxic (Batt and Kotkoskie, 1999). Collectively, these data indicate that C-A-P is a remarkably inert material when incorporated into diets fed to laboratory animals. In addition, clinical data from patients that were treated with pharmaceutical products containing C-A-P during a span of 5 decades indicates that there has been not one single adverse reaction reported that was attributed to the presence of C-A-P. Thus, all available data support the overwhelming safety of C-A-P for use as a pharmaceutical excipient. **Hypromellose Phthalate (HMP, a.k.a HPMCP)** **The molecular weights of polmers have been recognized to be several thousand Daltons. In 1984, the U.S. EPA established 1000 Daltons as the threshold for exempting polymers from genotoxicity evaluations. Furthermore, the EPA concluded that "substances with molecular weights greater than 400 are not readily absorbed through the intact skin and that substances with molecular weights greater than 1000 are not readily absorbed through the gastrointestinal tract" (49 FR, No. 226, Nov 21, 1984). The molecular weight of hypromellose phthalate (HPM) has been calculated to be in the range of 38,000 to 60,000 Daltons (Fukasawa and Obara, 2003).** **1) Molecular weight** Results for molecular weight determination depend on method of measurement. The most recent study (Fukasawa and Obara, 2003) used GPC-MALLS and the results were about 38000-60000 as Mw (Molecular weight – weight based) and 15000-26000 as Mn (Molecular weight – number based). Kato's study (**Kato *et al.*, 1982**) shows about 45000-76000 as Mw and 13000-22000 as Mn, which were determined using GPC-LALLS. Rowe's study (Rowe, 1982) showed about 130000 – 210000 as Mw, which was measured by a relative	

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	method using polystyrene standards. 2) **Toxicological studies** In the acute study in rats (**Kitagawa *et al.*, 1970**), LD_{50} could not be determined (presumably over 15 g/kg). In the subacute study in rats for 30 days, dosing up to 10 g/kg/day, there were no adverse effects (**Kitagawa *et al.*, 1970**). In the chronic study in rats, dosing up to 6 g/kg/day for 6 months, there was no remarkable toxicity (**Kitagawa *et al.*, 1970**). Another chronic study using dogs, dosing up to 3 g/kg/day 53 weeks was conducted (**Woodward Research, 1974**). There were no changes in the dogs which could be ascribed to the administration of HMP with the exception of a frequent occurrence of soft stools for dogs receiving 3 g/kg/day and a less frequent occurrence for dogs receiving 1.5 g/kg/day. In the teratogenicity study using rats and mice, dosing 2.4 g/kg (rat) and 4 g/kg (mouse), it can be concluded that HMP produces no malformation (**Ito and Toida, 1972**). Two ADME studies in rats were conducted using ^{14}C-labeled HMP (**Kitagawa *et al.*, 1971, 1974**). One was with ^{14}C labeled to methoxy groups of the HPMC backbone, dosing 3 g/kg. Approximately 92-96 % of the doses were excreted in feces within 96 hrs, and less than 1 % of HMP was excreted in urine. Another study was conducted using ^{14}C labeled to the phthalyl groups, at a dose of 1.3 g/kg. Excretion in the urine was 0.7 % for male and 1.2% for female rats during 72 hrs, whereas excretion in the feces was 95 % for male and 91 % for female rats. These studies indicated poor oral absorption for this high molecular weight polymer as predicted by the EPA FR notice. This polymer is a component of Zentase a pancreatic enzyme preparation and was submitted to FDA in NDA 22,210, December 17, 2007. Consumption of the highest dosage	

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	of 20,000 USP lipase units would cause the patient to ingest 25 capsules as the estimated maximum daily consumption. Lower strength capsules could allow a greater number of capsule ingestions per day to reach the maximum recommended daily dose. The approved oral formulations of HPMCP by the FDA are up to 302.4 mg/unit dose. The maximum daily acceptable oral level is not available. **Polyvinylacetate Phthalate (PVAP)** Polyvinyl acetate phthalate (PVAP) has been used in the pharmaceutical industry since the late 1960's as an enteric polymer in coating systems for oral solid dosage forms and in monogramming inks for marking capsules for prescription drugs and over-the-counter (OTC) drugs. PVAP is an enteric polymer manufactured from the catalytic esterification of polyvinyl alcohol (PVA) with phthalic anhydride. PVAP is a partially substituted polyvinyl acetate polymer that has been modified by the addition of phthalate groups that form an ester linkage with the hydroxyl groups present on the polyvinyl acetate polymer. It contains not less than 55% and not more than 62% of phthalyl (0-carboxybenzoyl C_8 H_5 0_3) groups. PVAP is also available as a co-processed excipient with titanium dioxide to produce polyvinyl acetate phthalate and titanium dioxide (PVAP-T). Titanium Dioxide USP-NF (TiO_2) is incorporated into the PVAP polymer matrix during polymer formation. The incorporation of the TiO_2 inside the polymer matrix provides unique properties which differ from simple blending of the two materials. The co-processed product is then micronized to achieve a target particle size. A monograph with official standards for PVAP is included in the United States Pharmacopeia/National Formulary (USP-NF). PVAP-T meets all of the NF specifications for	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	PVAP except residue on ignition (due to the presence of TiO_2). An IPEC member company [4] (manufacturer of PVAP and PVAP-T) sponsored several studies, all consistent with current Good Laboratory Practice (GLP) and internationally recognized guidelines, to provide safety data to support current and new applications for PVAP and PVAP-T. The new studies included an acute oral toxicity study, a 90-day subchronic dietary study in rats, a developmental toxicity study in rats and two genotoxicity tests. The acute oral toxicity of PVAP was assessed in male and female rats that received PVAP by gavage at the maximum (limit) dose. Under the conditions of the study, the acute oral LD50 of PVAP was estimated to be greater than 5000 mg/kg in the rat. A 90-day subchronic dietary study was conducted to evaluate the potential toxicity of PVAP when administered in the diet to Sprague Dawley CRL: CD (SD) rats (20/sex/group) at a dietary concentration of 0.75%, 1.5% and 5.0% for a minimum of 90 days. Control animals (20/sex) received untreated standard laboratory diet. Daily administration of PVAP in the diet was well tolerated in male and female rats up to a concentration of 5%. No PVAP-related toxicity or mortality was observed. Based on these results, the no-observed-adverse-effect level (NOAEL) was the 5% dietary concentration. A developmental toxicity study was conducted to assess the potential toxicity of PVAP in Crl: CD (SD) presumed-pregnant female rats (from implantation to closure of the hard palate). This study was consistent with the ICH Harmonized Tripartite Guideline stages C and D of the reproductive process. There were no consistent, treatment-related, dose-dependent, statistically significant adverse effects on any of the maternal and fetal parameters evaluated. Therefore, the maternal and developmental no-observable-adverse-effect level (NOAEL) of PVAP is the highest concentration administered 3.0%. A bacterial mutation test and a chromosome aberration test were performed to evaluate the	

[4] Data supplied by Colorcon

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	potential genotoxicity of PVAP. There was no evidence of genotoxic activity of PVAP in the *in vitro* bacterial mutation test and no evidence of clastogenicity in the *in vitro* chromosome aberration test for induction of chromosome damage. IPEC-Americas is concerned with the recent EMA determination that the PDE for Polyvinyl Acetate Phthalate (PVAP) is limited to 2 mg/kg/day as we are aware that currently marketed products in the EU already exceed the proposed maximum exposure level. New PVAP studies include a 90-day sub-chronic dietary study in rats, a developmental toxicity study in rats and two genotoxicity tests. The new studies provide additional safety information to support the commercial uses of PVAP in oral solid dosage forms for pharmaceutical applications. In addition, an acute oral toxicity study and a bacterial mutation test were conducted with PVAP-T. A copy of the study reports were provided to EMA in confidence. The study results are summarized below. The results of the new studies should be used to determine the Permitted Daily Exposure (PDE) for PVAP. **PVAP Toxicology Study Results** The IPEC member company sponsored several studies, all consistent with current Good Laboratory Practice (GLP) and internationally recognized guidelines, to provide safety data to support current and new applications for PVAP and PVAP-T. The new studies included an acute oral toxicity study, a 90-day subchronic dietary study in rats, a developmental toxicity study in rats and two genotoxicity tests. The acute oral toxicity of PVAP was assessed in male and female rats that received PVAP by gavage at the maximum (limit) dose. Under the conditions of the study, the acute oral LD50 of PVAP was estimated to be greater than 5000 mg/kg in the rat. A 90-day subchronic dietary study was conducted to evaluate the potential toxicity of PVAP when administered in the diet to Sprague Dawley CRL: CD (SD) rats (20/sex/group) at a	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	dietary concentration of 0.75%, 1.5% and 5.0% for a minimum of 90 days. Control animals (20/sex) received untreated standard laboratory diet. Daily administration of PVAP in the diet was well tolerated in male and female rats up to a concentration of 5%. No PVAP related toxicity or mortality was observed. Based on these results, the no-observed-adverse-effect level (NOAEL) was the 5% dietary concentration. A developmental toxicity study was conducted to assess the potential toxicity of PVAP in Crl: CD (SD) presumed-pregnant female rats (from implantation to closure of the hard palate). This study was consistent with the ICH Harmonized Tripartite Guideline stages C and D of the reproductive process. There were no consistent, treatment-related, dose-dependent, statistically significant adverse effects on any of the maternal and fetal parameters evaluated. Therefore, the maternal and developmental no-observable-adverse-effect level (NOAEL) of PVAP is the highest concentration administered 3.0%. A bacterial mutation test and a chromosome aberration test were performed to evaluate the potential genotoxicity of PVAP. There was no evidence of genotoxic activity of PVAP in the *in vitro* bacterial mutation test and no evidence of clastogenicity in the *in vitro* chromosome aberration test for induction of chromosome damage. **PVAP-T Toxicology Study Results** The member company conducted two GLP studies to provide further supporting information for the safety of PVAP-T. An acute oral toxicity study and a genotoxicity test were conducted. The acute oral toxicity of co-processed Polyvinyl Acetate Phthalate and Titanium Dioxide (PVAP-T) was assessed when administered by gavage as a single oral dose to Sprague Dawley male and female rats. There were no deaths and no signs of intoxication. The acute oral LD_{50} of PVAP-T was estimated to be greater than 5000 mg/kg in the rat, the highest dose tested and the recommended limit dose. A bacterial mutation test was performed to evaluate the potential genotoxicity of PVAP-T. PVAP-T did not show any evidence of genotoxic activity. It may be concluded that PVAP-T is not genotoxic.	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	Analytical Studies to Bridge PVAP-T to the PVAP Studies The toxicological data for PVAP is used to support the safety of PVAP-T. In order to bridge PVAP-T to the PVAP data, several analytical studies were performed to demonstrate that PVAP and Titanium Dioxide (TiO_2) are not chemically altered during the manufacturing process or during transit through the gastrointestinal tract. A study report was submitted to the EMA. PVAP-T is essentially equivalent to PVAP and TiO_2 since the chemical composition, physiochemical properties and specifications of the PVAP and TiO_2 are unchanged during manufacture of PVAP-T. The toxicological/safety data that support the safety of PVAP can be used to support the safety of PVAP-T when used as an excipient. **Independent Expert Safety Evaluation of PVAP and PVAP-T** The New Excipient Evaluation Committee (NEEC) Expert Panel independently and collectively critically evaluated the data and information summarized for PVAP and PVAP-T and concluded that PVAP and PVAP-T are safe for their intended use as an excipient in pharmaceutical applications. Based on the toxicology study results, safety assessment and the estimated exposure assessment in the NEEC's report for PVAP and PVAP-T, the expert panel concluded that PVAP and PVAP-T could safely be used in drug products up to 829 mg per day. **PVAP Summary and Conclusion** The series of safety studies conducted with PVAP include a definitive 90-day subchronic toxicity study, a developmental toxicity study and several genotoxicity tests. There were no adverse effects reported in the 90-day subchronic toxicity study and the developmental toxicity study. PVAP was not genotoxic. The no-observed-adverse-effect level (NOAEL) in the GLP 90-day subchronic study was the 5% dietary concentration, which corresponds to a	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	dose of 3.12 g/kg/day for males and 3.64 g/kg/day for females, the highest level tested. The chemical composition, physiochemical properties and specifications of PVAP-T are unchanged during manufacturing process based on the analytical studies conducted.. Therefore, the toxicological data that support the safety of PVAP can be used to support the use of PVAP-T as an excipient. **Based on the toxicology study results, safety assessment and the estimated exposure assessment in the NEEC's report for PVAP and PVAP-T, the expert panel recommended that PVAP and PVAP-T could safely be used in drug products up to 829 mg per day.** **Conclusion** IPEC-Americas request that the EMA clarify that the "Guideline on the use of phthalates as excipients in human medicinal products" (EMA/CHMP/SWP/362974/2012) applies to only DBP and DEHP, and not to commonly used excipients such as C-A-P, PVAP, and HMP. These phthalate-containing excipients are substances in which the phthalate moiety is esterified with polymers and not the short chain alcohols that are used in the manufacture of DBP and DEHP which indicates the vast differences in toxicity among the two types of phthalate-containing chemicals. Available toxicological data indicate that these structurally diverse polymers have a potential for oral toxicity, which is in alignment with the EPA's conclusion of low polymer toxicity based on the compounds having molecular weights above 1000 Daltons. The series of safety studies that were conducted with PVAP include a definitive 90-day subchronic toxicity study, a developmental toxicity study and several genotoxicity tests. There were no adverse effects reported in the 90-day subchronic toxicity study and the developmental toxicity study. PVAP was not genotoxic. The no-observed-adverse-effect level (NOAEL) in the GLP 90-day subchronic study was the 5% dietary concentration, which corresponds to a dose of 3.12 g/kg/day for males and 3.64 g/kg/day for females, the	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	highest level tested. The chemical composition, physiochemical properties and specifications of PVAP-T are unchanged during manufacturing process based on the analytical studies. Therefore, the toxicological data that support the safety of PVAP can be used to support the use of PVAP-T as an excipient. Based on the toxicology study results, safety assessment and the estimated exposure assessment in the NEEC's report for PVAP and PVAP-T, the expert panel recommended that PVAP and PVAP-T could safely be used in drug products up to 829 mg per day. IPEC-Ameriacs would like this to be considered in revising the PDE for PVAP and PVAP-T. **Reference List** The United States Pharmacopeia XXI/National Formulary XVI,(1985), The United States Pharmacopeial Convention, Inc., 12601 Twinbrook Parkway, Rockville, MD 20852. (1984,1983) + Ivii pp. 22 +ù 29.5 cm. ISBN 0-913595-04-7. $155.00 (1-year subscription). J. Pharm. Sci. **74**(9), 1030. Batt, KJ and Kotkoskie LA (1999). An Evaluation of Genotoxicity Tests With Aquateric-« Aqueous Enteric Coating. Inter. J. Toxicol. **18**(2), 117-122. Fukasawa M and Obara S (2003). Molecular Weight Determintion of Hypromellose Phthalate (HPMCP) using Size Exclusion Chromatgraphy with a Multi-Laser Light Scattering Detector, Chem. Pharm. Bull. **51**(11), 1301-1306. Hodge HC (1944). The Chronic Toxiciy OF Cellulose Acetate Phthalate in Rats and Dogs. J. Pharmacol. Exp. Therap. **80**(3), 250-255. Hodge HC, Forsyth HH, and Ramsey GH (1944). Clinical Tests of Cellulose Acetate Phthalate as an Enteric Coating. J. Pharmacol. Exp. Therap. **80**(3), 241-249. Ito R and Toida S (1972). Studies on the Teratogenicity of a New Enteric Coating	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
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Stakeholder no.	General comment (if any)	Outcome (if applicable)
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7	<u>Comment 1:</u> A concept paper has only been released on the need for revision of the guideline on excipients in the label and package leaflet of medicinal products for human use - CPMP/463/00 Rev.1 (EMA/CHMP/SWP/888239/2011). However, in view of the the recommendations proposed in this draft guideline the scope extends further than what is stated in this concept paper, specifically regarding the formulation changes for existing authorised medicinal products. <u>Comment 2:</u> The recommendations are ambiguous. In lines 253-254 it is stated that the recommendations should be considered, whereas lines 257-259 propose that formulation changes are expected to be implemented as necessary. <u>Comment 3:</u> The impact of the proposed recommendations is not clear. Before this guideline is adopted it should be investigated and communicated: 1. which medicinal products are expected to be affected 2. what the impact on the market will be. <u>Comment 4:</u> Changes to formulations may raise problems that may turn out difficult to resolve:	<u>Response to Comment 1:</u> Phthalates are the only excipient for which a CHMP guideline has been written including a PDE for DBP and DEP. For all other excipients of the annex to the excipients label guideline, the scope is different and limited to the labelling for patients (package leaflet and packaging) supported by a background review. The only exception is methyl- and propyl-parabens where a reflection paper is being produced. <u>Response to Comment 2:</u> Lines 253 states that the recommendations in the guideline should be considered a precautionary measure in the absence of clinical evidence of phthalate induced adverse effects in humans. Whereas

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	1. which alternative excipients are anticipated? 2. When another excipient is replacing a phthalate, will a BE study be required? What if old and new formulation are not bioequivalent?	the information in lines 257 – 259 stipulates the regulatory action required for products containing excipients at levels exceeding the PDEs established by the guideline (e.g. for DBP and DEP containing products. Therefore the two statements relate to different points/issues. <u>Response to Comment 3:</u> 1. The recommendations of this guideline will affect DBP and DEP containing products. It will be the responsibility of Marketing Authorisation Holders of DEP and DBP containing products to identify these products and ensure that the presence of DBP and DEP are at levels associated with exposures at or below the PDE. An exceedance of the PDE will have to be justified to the relevant competent authority and may be accepted on a case–by case basis depending on a number of factors such as use in patients with life-limiting conditions etc.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
		2. The decision to adopt a PDE for DBP and DEP is a precaution taken for the purposes of safeguarding public health, therefore the impact on the market cannot take precedence over actions taken to safeguard public health. <u>Response to Comment 4:</u> 1. Where necessary (phthalate above PDE), alternative excipients are encouraged. A section on the diverse functions of phthalates has been added in the guideline. The choice of an alternative excipient will have to be discussed on a case-by-case basis taking into account its function and safety. 2. Any concerns regarding changes to the formulation should be discussed with the relevant competent authority for the product.
8	With respect to the toxicity evaluation of cellulose acetate phthalate (CAP) (see 6.4, line 205) and hydroxypropyl methylcellulose acetate phthalate (HPMCP) (see 6.5, line 218), a possible generation of significant amounts of free phthalic acids following a cleavage of the ester during shelf life should be considered. This can be enhanced in formulations which	The safety of free phthalic acid was reviewed however a PDE was not established for Phthalic Acid due to the PhEur specifying a 1 to 3 % limit

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	contain a component for ester cleavage, e.g. lipases in pancreatin formulations. Literature: European Journal of Pharmaceutics and Biopharmaceutics 47 (1999), page 39 – 50 (see attachment). We propose that the toxicity potential of free phthalic acids as a result of instability of CAP and HPMCP would be added to the considerations about the toxicity evaluation, especially in relation to pancreatin products which are used for permanent, lifelong treatment.	for free phthalic acid for the phthalate polymers, low bioavailability and the the toxicity of phthalic acid being accounted for as a metabolite in the evaluation of the other phthalates.
9	Sanofi appreciates the opportunity to provide feedback on the draft guidance which is a significant step forward to determine the use of safe excipients in human medicinal products. We would like to offer the following comments: Clarity is needed to explain the term “phthalate” that may not have the same meaning across regions/companies and to define which phthalates or types of phthalates are of concern: • The U.S. Environmental Protection Agency (EPA) and other regulatory agencies have defined “phtalates” as diesters of orthophthalic acid. • Phthalate polymers that have been modified by esterification with *ortho*-phthalic acid groups, are occasionally assimilate to “phthalates” because they have the word “phthalate” in their names, while these high-molecular-weight polymers differ markedly from the short-chain alcohols used to produce *ortho*-phthalates, and their chemical properties are very different. • This draft guidance is focusing on selected phthalates without making differentiation between phthalate esters, (*ortho*-phthalate esters) and polymers while it seems that mainly *ortho*-phthalates are under scrutiny by health agencies	The executive summary of the guideline was updated to include a description of the term phthalates. It is correct that the polymers are not a significant concern and this is reflected by the absence of a PDE.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	It would be valuable to harmonize recommendations across regions • This document provide recommendations on the use of DBP, DEP and PVAP as excipients with PDE values of 0.01, 4 and 2 mg/kg/day respectively (and no specific recommendation for the use of CAP and HPMCP in the absence of potential concern for human safety) while the FDA in its guidance *"Limiting the Use of Certain phthalates as excipients in CDER Regulated Products*" issued in December 2012, provides recommendation to avoid the use of DPB and DEHP since alternatives usually exist and if an alternative cannot be used, to provide a justification for why DBP or DEHP should be used as well as a risk/benefit assessment. For DBP, although the FDA guideline does not mention a PDE for medicinal products, it mentions an EPA-recommended oral RfD (reference dose) of 0.1 mg/kg which is 10 times higher than the PDE recommended in the draft EMA guideline (0.01 mg/kg).	The fact that the PDE for DBP is stricter than the one in the FDA guidance is based on the method to calculate the PDE which takes into account currently available data which may not have been available earlier. DEHP is present only in devices which is not the scope of this guideline.
10	This guideline reviews scientific data on phthalates pharmacokinetics and their toxicity towards fertility and reproduction. While it seems acceptable to present in the guideline the most important conclusions or global evaluation of studies published in the scientific literature, in our opinion these data are presented in too much detail. The contents of this guideline seem to fit better a reflection paper than a guideline. Furthermore, important recent articles indicating reproductive and developmental toxicity of dibutyl phthalate (DBP) and describing hepatotoxicity studies for diethyl phthalate (DEP) were not taken into account, while from the toxicological point of view this portion of information is of high relevance when defining permitted daily exposure (PDE) values for pharmaceutical excipients. In addition, it is unclear how the requirements defined by this guideline will be implemented to EU members' local law to make the proposed limits binding.	Although the level of details could fit a reflection paper, this document provides PDE values for some of the phthalates aiming at a potential regulatory impact proper to guidelines. A review of the available literature reporting low dose hepatotoxicity of DEP was conducted. Much of this data was generated in a set of studies conducted by Pereira *et al* 2006-2008 which also showed peroxisome proliferation at doses associated with hepatoxicity. PPAR induced hepatotoxicity/carcinogenicity has

Stakeholder no.	General comment (if any)	Outcome (if applicable)
		been extensively researched and based on current knowledge is not considered to be relevant to man. In addition there were uncertainties regarding the reliability of the results generated by Pereira and co-workers as some of the studies reported effects that were inconsistent with the vast majority of data generated by other researchers (e.g. severe hepatotoxicity in rodents at exposures several fold lower than doses associated with little or no effect on the liver in other studies). Leading to questions regarding the adequacy/quality of the investigations performed and the reporting of the results. Due to these uncertainties and also lack of data showing clinical relevance these studies could not be used to derive the PDE for DBP or DEP. Any concerns regarding the implementation of the guideline should be discussed with the relevant competent authority for the product.
12	In Germany there is a list of medicinal products containing Dibutyl phthalate (DBP) and	It is acknowledge that there many

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	Diethyl phthalate (DEP). This list is based on ABDA database (The ABDA databases are official German databases only for healthcare professionals, which contain comprehensive data concerning medicinal drugs and substances as well as drug-related information). However, it seems that not all listed medicinal products mention phthalates in their respective SPC (section list of excipients). Subsequently if such declaration of phthalates as allowed excipients in SPC / Leaflet is not mandatory, due to the right of information of healthcare professionals as well as patients / customer, this declaration should be an obligation. Already in 1999, most of phthalates in certain toys and childcare articles were prohibited (1999/815/EC). In 2004, the ban was extended to all toys and childcare articles (2004/781/EG). Also in 2004 the prohibition in cosmetic products and limited use in other consumer products such as paints and adhesives (2004/93/EC) followed. So it is questionable why phthalates are still tolerated in medical devices (DEHP) as a plasticizer as well as in in drugs as adjuvant. Phthalates are widely used in food industry suggesting a high exposition of people with Phthalates every day. In this draft version there is no information which compare the exposition of people from products of food industry to the potential exposition from medicinal products. If there should be differences of several orders of magnitude strict low limits for Phthalates in medicinal products don't reduce the risk for patients while the costs for searching, investigating and testing alternatives are probably very high. Furthermore because of high costs a lot of older and well established products will be withdrawn from the market. It should be noted in this context that appropriate alternatives as excipients should exist. Phthalates, especially in combination with various polymers, may be used as plasticizers and film coating agents in orally ingested solid pharmaceutical dosage forms and in numerous types of modified-release drug delivery systems such as enteric-coated and delayed-release tablets, pelletized delayed-release capsules, enteric-coated capsules, and controlled-release	sources of phthalate exposure other than medicines. As mentioned in the guideline PDE values have been determined as a precautionary measure. The clinical relevance of phthalate induced endocrine disruption is unclear due to conflicting data on effects in humans. For this reason the PDEs for DBP and DEP were based exclusively on preclinical data. Updates to the clinical sections of the SPC (sections 2 through to 5.1), label and patient information leaflet are usually based on clinical data, not preclinical data, therefore updates to these sections of the product information has not been recommended if below the PDE. In the case of an exceedance of the PDE of DBP and DEP (which can be accepted on a case-by case basis depending on the benefit/risk to the patient population and possible difficulties in finding an alternative excipient) it is recommended that sections 2, 4.6 and 5.3 of the SPC be

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	transdermal films. These phthalate related properties have to replace by an appropriate alternative excipient, so that pharmacological profile (Pharmacokinetics as well as Pharmacodynamics) of the product will not change. According to guideline draft, EMA proposed a wording for the product information of phthalate-containing medicinal products, to be incorporated in the next revision of the "Guideline on Excipients in the Label and Package Leaflet of Medicinal Products for Human Use (CPMP/463/00 Rev.1)". Due to the fact that phthalates are associated with effects on reproduction and development in relation to their hormonal (anti-androgenic) properties, note of phthalate and their harmful properties should listed not only under excipients, but also under section "special warning" and / or "pregnancy and lactation". The idea to define PDEs for DBP, DEP or PVAP each if presented in medicinal products is good, but it will be difficult to realise. Since the recommended daily dose of several drugs could be very variable – in dependence on for example severity of symptoms / disorder etc. or in dependence on indication – the resulting amount of respective phthalate in patient could not meet the corresponding and allowed PDE. Therefore the PDE have to calculate on the basis of maximum dosage / day and with respect of mean minimum weight of patient	updated as appropriate.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 26, 37, 58, and 218	1	Comments: HPMCP is misleadingly described as “hydroxypropyl methylcellulose acetate phthalate”. The correct chemical name for HPMCP is “hydroxypropylmethylcellulose phthalate” (CAS Registry Number: 9050-31-1). Proposed change (if any): Hydroxypropyl-~~-~~methylcellulose ~~acetate~~ phthalate (HPMCP)	Accepted.
Line 26	2	Proposed change (if any): 6.5. Hydroxypropyl-methylcellulose ~~acetate~~ phthalate (HPMCP) 7	Accepted.
Lines 32-37	3	Comments: There is a major difference between low molecular weight phthalates and high molecular weight polymeric phthalates. Phthalates (phthalates esters) such DBP is a very specific diester of benzenedicarboxylic acid. Enteric polymers such as PVAP are polymers that are partially esterfied with phthalate groups. Proposed change (if any): We request that EMA provide an explanation in the guidance document explaining the differences between	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		the low molecular weight materials such as DBP and high molecular weight enteric polymers such as PVAP.	
Lines 32-37	6	Comments: There is a major difference between low molecular weight phthalates and high molecular weight polymeric phthalates. Phthalates (phthalates esters) such as DBP is a very specific diester of benzenedicarboxylic acid. Enteric polymers such as PVAP are polymers that are partially esterfied with phthalate groups Proposed change (if any): We request that EMA provide an explanation in the guidance document explaining the differences between the low molecular weight materials such as DBP and high molecular weight enteric polymers such as PVAP.	Accepted.
Lines 35 - 37	2	Proposed change (if any): remains to be established. The most commonly used phthalates in medicinal products licensed in the EU are: dibutyl phthalate (DBP), diethyl phthalate (DEP), polyvinyl acetate phthalate (PVAP), cellulose acetate phthalate (CAP), and hydroxypropyl-methylcellulose ~~acetate~~ phthalate (HPMCP).	Accepted.
Lines 40-42	3	Comments: The PDE for PVAP can be changed based on the new toxicological studies provided to EMA.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): see revised PDE for PVAP below	
Lines 40-42	6	Comments: The PDE for PVAP should be changed based on the new toxicological studies provided to EMA. The PDEs listed in the document are incorrect and based on old safety data. To adequately describe current uses of PVAP, the PDE should be changed to reflect the current safety data which exists Proposed change (if any): see revised PDE for PVAP below	Accepted.
		Comments: PDE values for DBP and DEP should be re-evaluated according to the most recent data for DBP and hepatotoxicity reports for DEP (please see the comments below for details).	Accepted. The PDE values were re-evaluated and the final PDE values were adopted following the re-evaluation of data.
Line 41	10	Comments: Proposed change (if any):	
Lines 56 - 59	2	Proposed change (if any): Based on a survey involving the EU Member States	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		(unpublished), the most commonly used phthalates in medicinal products licensed in the EU are: cellulose acetate phthalate (CAP), diethyl phthalate (DEP), hydroxypropyl-methylcellulose ~~acetate~~ phthalate (HPMCP), polyvinyl acetate phthalate (PVAP) and dibutyl phthalate (DBP).	
Lines 69-75	10	Comments: Treatment period for given medicinal product should also be taken into account, as the number of studies with low phthalate doses show their toxicity after prolonged period of administration. Therefore, for products indicated for single or short-term administration, it is proposed to allow justification based also on the administration period. Proposed changes: The following sentence is proposed to be added in line 75: <u>Phthalates use may be also justifiable whenever given medicinal product is indicated for single- or short-term use.</u>	Partially accepted. The guidelines states that the exceedance of the PDE can be accepted on a case-by case basis and this includes consideration of the exposure duration (i.e. short-term vs long-term)
Lines 137-160	10	Comments: According to recent article by Zhang et al. (Biomed Environ Sci, 2013; 26(1): 63-69), changes (up-regulation) in gonadotropin-releasing hormone receptor, progesterone receptor and androgen receptor genes expression were observed after 90-day treatment of young SD rats with DBP in the dose of	Partly accepted. This new data was taken into account in the re-review of the PDE of DBP.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		approx. 0,5 mg/kg/day. Although changes in genes expression do not directly lead to protein concentration/activity changes, this data show that sex hormone release regulation may be altered by the DBP dose as low as 0,5 mg/kg/day. Similarly, the work of Hu et al. (Toxicol, 2013; 314: 65–75) may also be discussed, where the LOAEL of 0,5 mg/kg b.w./day of DBP administered as s.c. injection advanced, among others, pubertal timing. Therefore, it is suggested that the proposed LOAEL (2 mg/kg b.w./day) and PDE for DBP (0.01 mg/kg/day) should be revised according to the most recent data published.	
Line 152	11	Comments: Comment: The DBP LOAEL from the Lee et al study is considerably lower than LOAELs/NOAELs determined in previous studies. This fact alone should trigger concern. Moreover, the validity of the Lee et al study has been extensively criticised particularly by various contributors to the EPA IRIS review of DBP. For example: The available data and discussion from study by Lee et al (2004) has many methodological and statistical issues. There is a lack of information on alternate effect on HPA-axis (alternate source of adrenal steroid production) as well as the role of chronological exposure. Thus EPA's decision not to use the	Not accepted. The concerns raised have been carefully reviewed. These concerns appear to be based on comments provided by 3 out of 6 experts selected to peer review the EPA's IRIS evaluation of DBP. The committee considered the comments of the peer review panel and re-evaluated the study be Lee et al 2004. Overall the committee considers that the results of the Lee et al (2004) study can be used to establish the PDE of DBP. Whilst it is agreed that this study had some limitations, these were not considered sufficient to justify the dismissal of findings

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		information to derive at RfD is appropriate. In addition, the FDA's recent evaluation does NOT use the Lee et al LOAEL and an RfD of 0.1 mg/kg/day has been determined: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM294086.pdf In the US the CSPC has determined a chronic limit of 0.2 mg/kg/day: http://www.cpsc.gov/PageFiles/126528/toxicityDBP.pdf IF SWP is still minded to use the Lee et al LOAEL, before proceeding, two actions are strongly recommended: • Raw data audit (to avoid issues similar to those related to the Oishi publication on propyl paraben) • Evaluation of data using criteria established by Lewis et al, 2002: http://tpx.sagepub.com/content/30/1/66.full.pdf Proposed change (if any): Since the Lee et al data are considered unreliable and have been subject to a significant number of adverse comments from relevant experts, an alternative more reliable NOAEL/LOAEL should be employed	that have been reproduced in a number of studies conducted with DBP, albeit at higher doses. In addition recent publications have demonstrated endocrine effects at doses equivalent to the effects reported in the Lee et al 2004 study which supports the evidence of low dose effects of DBP. For these reasons the PDE for DBP has been formally adopted in the finalised guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 195-204	3	Comments: This entire section should be revised to include reference to Colorcon's new toxicological studies for PVAP and PVAP-T. Proposed change (if any): The new PVAP studies included a 90-day sub-chronic dietary study in rats, a developmental toxicity study in rats and two genotoxicity tests. An acute oral toxicity study and a bacterial mutation test were also conducted with PVAP-T.	Accepted.
Lines 195-204	6	Comments: This entire section should be revised to include reference to Colorcon's new toxicological studies for PVAP and PVAP-T. Proposed change (if any): The new PVAP studies included a 90-day sub-chronic dietary study in rats, a developmental toxicity study in rats and two genotoxicity tests. An acute oral toxicity study and a bacterial mutation test were also conducted with PVAP-T.	Accepted.
Line 218	2	Proposed change (if any): *6.5. Hydroxypropyl-methylcellulose ~~acetate~~ phthalate (HPMCP)*	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 223	10	Comment: A new section of the guideline is proposed to be added as important hepatotoxicity data for DEP should also be discussed and taken into account. According to the work of Pereira et al. (Regul Toxicol Pharmacol. 2006 Jul;45(2):169-77), p.o. treatment with DEP at doses 2,85 mg/kg b.w./day and lower results in mitochondrial proliferation as well as accumulation of glycogen, cholesterol and triglycerides within the liver. Exposure to lower concentration (0.57 mg/kg b.w./day) for 5 months results in the increase in peroxisome numbers leading to severe hepatocellular changes, elevated serum and liver enzyme levels and impaired metabolism of glycogen, cholesterol and triglyceride as well as altered liver histology. Similar findings were reported by Pereira et al. (Environ Toxicol Pharmacol. 2007;23(3):319-27), Pereira and Rao (Environ Toxicol Pharmacol. 2006 Jan;21(1):93-102) as well as Sinkar and Rao (Toxicological & Environmental Chemistry, 2007;89(1): 173-183). DEP hepatotoxicity was shown also in chronic toxicity study in mice fed for 90 days with doses of 1.25, 3.13 and 6.25 mg/kg b.w./day by Mapuskar et al. (Pesticide Biochemistry and Physiology, 2007; 87(2):156-163). Furthermore, DEP present in the diet at similar concentration as in studies above resulted in	Not accepted. As discussed previously the data generated by Pereira and co-workers were considered unreliable and therefore could not be used to establish the PDE of DEP.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		vacuolations and degeneration in the zona fasciculata region of the adrenal cortex of F0, F1 and F2 male rats generations, according to Pereira et al. (Toxicology International, 2008; 15(1):63-67). Taking into account the presence of sound hepatotoxicity data for DEP in the scientific literature, the analysis of these data should be performed and discussed in the guideline. On this basis, a re-evaluation of permitted daily dose of DEP should be performed.	
Lines 233-238	10	Comments: The conclusion on DEP PDE should be revised since the hepatotoxicity was reported for DEP doses of 0.57-6.25 mg/kg b.w./day in several chronic toxicity studies.	Not accepted - as discussed above.
Lines 224-251	10	Comments: Inclusion of a table summarising permitted daily doses in pharmaceutical products in the conclusion section will be very useful. Since PDEs are the most important information in the guideline, it is suggested to make these data easy to be found and interpreted.	Accepted
Line 232	11	Comments: ICH Q3C (R5)	Agreed. Will be corrected
Lines 239-244	3	Comments: Comment: The appropriate PDE should be calculated from the NOAEL from Colorcon's developmental	Partly accepted. Based on the findings of the new developmental toxicity study the provisional PDE of PVAP was removed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		toxicity study. The NOAEL is 2324.6 mg/kg/day. Proposed change (if any): Using an uncertainty factor of 5 for interspecies variation and 10 for intraspecies variation results in a PDE of 46.5 mg/kg/day for PVAP and PVAP-T.	
Lines 239-244	6	Comments: The appropriate PDE should be calculated from the NOAEL from Colorcon's developmental toxicity study. The NOAEL is 2324.6 mg/kg/day. Proposed change (if any): Using an uncertainty factor of 5 for interspecies variation and 10 for intraspecies variation results in a PDE of 46.5 mg/kg/day for PVAP and PVAP-T.	Partly accepted – see above.
Lines 245-251	10	Comments: The conclusion on DEP PDE should be revised since the hepatotoxicity was reported for DEP doses of 0.57-6.25 mg/kg b.w./day in several chronic toxicity studies.	Not accepted – see above
Line 251	11	Comments: See comments above regarding issues with Lee et al, 2004, LOAEL	Not accepted.
Lines 257-259	12	Comments: According to guideline draft for existing authorised medicinal products, it is proposed to set a time limit of	It is understandable that various issues which can impact on the implementation time may occur. In this case, the applicant should discuss with the relevant regulatory authority

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		3 years (after coming into force of the final guideline) for the implementation of formulation changes and consequential regulatory applications, as necessary. Proposed change (if any): In exceptional cases special agreements between MAH and respective regulatory authority concerning the timeline of implementation of formulation changes should be allowed (e.g. if changes in manufacturing process of drug results in problems regarding the quality / stability /efficacy of the drug)	and find an agreed implementation time based on the individual justification prior the due date.
Lines 260-263	10	Comments: Please refer to the comment to lines 69-75. Proposed changes: The presence in medicinal products of DBP, DEP or PVAP at levels giving rise to daily exposures above the PDEs could be accepted as exceptions, on a case-by-case basis taking into consideration the intended patient population, the disease seriousness, the administration period and the presence or not of alternative treatment options.	Partially accepted. It is agreed that the duration of exposure is clinically relevant. This is taken into consideration in the calculation of the PDE (variable “F3” in ICH Q3C) and therefore not repeated here.