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Guideline on the use of phthalates as excipients in human medicinal products

Draft

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Executive summary

Literature data in animals show that certain phthalates are associated with effects on reproduction and development in relation to their hormonal (anti-androgenic) properties. Currently available human data on the impact of phthalate exposure are limited and therefore the clinical relevance of such findings 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).

The review of data concluded that there are, presently, no data indicating that the presence of CAP and HPMCP in human medicinal products constitutes a potential risk for human safety.

For DBP, DEP and PVAP, adverse reproductive and/or developmental effects have been observed in non-clinical studies and as a consequence, Permitted Daily Exposures (PDE) values of 0.01, 4 and 2 mg/kg/day for DBP, DEP and PVAP respectively are proposed.

These recommendations are precautionary measures aiming at reducing the phthalate content of medicines in order to ensure safety in all types of patient populations. 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.

1. Introduction

The European Commission has decided to revise the “Guideline on excipients in the label and package leaflet of medicinal products for human use (CPMP/463/00)” and a concept paper on the need for such revision has been published in 2012 (EMA/CHMP/SWP/888239/2011). Phthalates used in medicinal products is one of the priority among excipients under revision.

During the last two decades, phthalate esters have attracted the special attention of the scientific community, regulatory agencies and the general public as a consequence of their widespread use and possible endocrine effects (Talsness et al. 2009). Certain phthalates are used as excipients in medicinal products: mainly in the enteric film coating of modified-release tablets and capsules (see section 4). Based on a survey involving the EU Member States (unpublished), the most commonly used phthalates in medicinal products licensed in the EU are: cellulose acetate phthalate (CAP), diethyl phthalate (DEP), hydroxypropyl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).

DBP has been classified by the European Commission as a reprotoxic substance on the basis of non-clinical data (Regulation No 1272/2008). The use of DBP is regulated within various areas while no restrictions have been put on the use of CAP, DEP, HPMPC and PVAP. Hence, DBP is prohibited in cosmetic products within the EU (Directive 76/768/EEC) and the use of DBP has been restricted in toys and childcare articles (Directive 2005/84/EC). Moreover, the European Food Safety Agency (EFSA) has restricted the presence of DBP in plastic which comes into contact with food. With respect to medical devices, all devices containing DBP are to be labelled and the manufacturers should justify its presence in devices intended for use in children, pregnant or nursing women (Directive 2007/47/EC). Furthermore, the Directive encourages the replacement of phthalates in medical devices.

The CHMP article 5(3) scientific opinion on ‘The Potential Risks of Carcinogens, Mutagens and Substances Toxic to Reproduction (CMR) When These Are Used as Excipients in Medicinal Products for Human Use’ states under section 4 “Any risk identified for an excipient and in particular a CMR substance, would be acceptable only on condition that this excipient cannot be substituted with a safer available alternative, or that the toxicological effects in animal models are considered not relevant for

humans (e.g. species specific, very large safety ratio) or where the overall benefit/risk balance for the product outweighs the safety concern with the product". Hence, it is encouraged to replace potentially toxic excipients with safer alternatives, as it cannot be excluded that the adverse effects caused by the excipient in non-clinical studies on reproduction and development are of clinical relevance.

2. Scope

This guideline covers the phthalates most commonly used as excipients in medicinal products authorised in the EU.

The recommendations provided in this document apply to new and existing marketed medicinal products.

3. Legal basis

This guideline has to be read in conjunction with Annex I (Part 1) of Directive 2001/83/EC. This guideline should be read in conjunction with the relevant EMA CHMP/EC documents with special emphasis on:

- CHMP scientific article 5(3) opinion the potential risks of carcinogens, mutagens and substances toxic to reproduction when these substances are used as excipients of medicinal products for human use.(EMEA/CHMP/SWP/146166/2007)
- Note for guidance on impurities: residual solvents (CPMP/ICH/283/95).
- Guideline on excipients in the label and package leaflet of medicinal products for human use (CPMP/463/00 Rev.1).
- Concept paper 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)
- Guideline on Summary of Product Characteristics[1] (2009, Rev.2)

4. Pharmaceutical uses of phthalates

Phthalates are used as functional excipients in a large number of oral pharmaceutical formulations. They are most commonly used as plasticizing agents in enteric film-coating materials or as a matrix binder for tablets, capsules, beads and granules. Due to their plasticizer properties, phthalates can be included in soft gelatine capsule formulations. They may also be used to control the viscosity of certain liquid formulations. Phthalates confer the following properties to tablets and capsules:

- Resistance to degradation of the tablet/capsule coating in the acidic environment of the stomach during transit to the site of absorption in the intestine. The solubility of the phthalates at neutral and high pHs, and insolubility at low pHs protects the tablet during prolonged contact with acidic gastric juices and ensures its dissolution in the neutral environment of the intestines.
- Maintenance of flexibility of solid dosage forms (e.g. tablet/capsules) for quality purposes (e.g. to prevent cracking) and to enhance oral administration (e.g. increased ease of swallowing).
- Viscosity modification during production of pharmaceutical formulations to control characteristics such as thinness of the sealing coat whilst maintaining adequate barrier to moisture.
- Control of drug-release characteristics of modified-release preparations.

[1] http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf

- Increase of the palatability of bitter tasting formulations by effectively sealing off the underlying drug formulation (the phthalates are tasteless and odourless).

5. Pharmacokinetics

Following oral administration of ^{14}C-DEP to mice and rats, the majority of the administered dose was excreted in the urine (82%) within 24 hours post-dosing (Api, 2001). The major metabolite detected in the urine was the ester hydrolysis product, monoethyl phthalate (MEP). Phthalic acid was also detected in urine as a minor metabolite. The metabolism of DEP appears to be similar in rodents and humans. Hence pancreatic insufficient cystic fibrosis children taking oral capsules formulated with DEP had significantly higher levels of MEP and MEP-glucuronide in the urine than untreated children (Keller et al. 2009).

Following oral administration of ^{14}C-DBP to rats and hamsters, DBP was readily absorbed from the gastrointestinal tract. DBP and its metabolites are rapidly excreted hence more than 90% of the administered radioactivity was detected in the urine within 48 hours (EU Risk Assessment Report – Dibutyl phthalate). Similarly in humans, around than 90% of the administered DBP is excreted in the urine within 24 hours in the form of metabolites (Koch et al. 2012). The DBP metabolites that occur in rat urine are mono-butyl phthalate (MBP), MBP-glucuronide and various oxidation products of MBP. Children and adults taking oral capsules formulated with DBP had high urinary levels of MBP–glucuronide and free MBP (Keller et al. 2009, Seckin et al. 2009). These data indicate that the major DBP metabolites are formed in both rodents and humans.

The metabolites of several phthalates, including the DBP metabolite MBP, have been detected in the amniotic fluid of pregnant women indicating that exposure to DBP can occur *in utero* (Huang et al. 2009, Wittassek et al. 2009, Jensen et al. 2012). Moreover, DBP has been identified in human breast milk which suggests that breastfeeding may be a source to infant phthalate exposure (Zimmermann et al. 2012).

No pharmacokinetic data is available for CAP, HPMPC and PVAP.

6. Data on reproductive and developmental toxicity

6.1. Dibutyl phthalate (DBP)

DBP was associated with an anti-androgenic effect in a human cell line as it inhibited the binding of dihydrotestosterone to the androgen receptor with an IC_{50} of 74 µM (Christen et al. 2010). DBP was devoid of oestrogenic activity *in vitro* (Lee et al. 2012). It is presently believed that DBP disrupts the development of androgen-dependent structures in animals by inhibiting fetal testicular testosterone biosynthesis. Hence, administration of DBP to pregnant rats on gestation day 8 through 18 induced a dose-related decrease in fetal testosterone production at doses above 300 mg/kg body weight/day (Howdeshell et al. 2008). A dose-additive effect on fetal testosterone production was observed when combining several different phthalates (Howdeshell et al. 2008; Hannas et al. 2011).

A LOAEL of 2 mg/kg body weight/day was derived from a developmental toxicity study where rats received DBP via the diet from late gestation (gestation day 15) to the end of lactation (postnatal day 21) (Lee et al. 2004). Treatment-related findings included a reduced male birth ratio, decreased male anogenital distance and retention of nipples, reduction of testicular spermatocyte development as well as mammary gland changes at low incidence in both sexes. In the adult stage, testicular and epididymal lesions were evident. A decreased number of spermatocytes in the seminiferous tubules was evident at the LOAEL.

Several other reliable reproduction and developmental toxicity studies in mice and rats applying oral DBP dosing have shown effects on fertility (e.g., reduced fertility due to testicular atrophy and reduced sperm production), embryo-fetal toxicity (e.g., decreased number of litters/pair and live pups/litter), and external, skeletal and visceral malformations (e.g., cleft palate, fusion of the sternebrae, cryptorchidism, hypospadias or agenesis of the prostate, epididymus and vas deferens). Based on studies performed in rats, LOAELs for embryo-fetal and developmental toxicity of 52 and 100 mg/kg body weight/day, respectively, has been established (see EU Risk Assessment Report – Dibutyl phthalate, 2003; 2004 for further details).

Some clinical studies indicate an association between the level of the DBP metabolite MBP present in prenatal maternal urine samples and reduced anogenital distance in male newborns (Swan et al. 2005, 2008). This finding has however not been confirmed by others (Suzuki et al. 2012; Huang et al. 2009).

6.2. Diethyl phthalate (DEP)

It was shown that DEP inhibits the binding of dihydrotestosterone to the androgen receptor with an IC_{50} of 515 µM and is hence associated with a weak anti-androgenic effect (Christen et al. 2010). In concordance with this finding, a low binding affinity for the androgen receptor has been reported for DEP in a competitive binding assay (IC_{50} of 0.84 mM) (Fang et al. 2003). Moreover, DEP was devoid of oestrogenic activity *in vitro* (Lee et al. 2012). Administration of DEP to rats on gestation day 8 through 18 did not affect the fetal testosterone production at doses up to 900 mg/kg body weight/day (Howdeshell et al. 2008).

In an extended GLP-compliant two-generation reproductive toxicity study in rats, administration of DEP via the diet gave rise to an increased incidence of abnormal sperm at 3000 ppm (222 mg/kg/day) and 15,000 ppm (1150 mg/kg/day) in F1 males (Fujii et al. 2005). This finding was not considered toxicologically significant because of the lack of effects on reproductive parameters such as copulation and fertility indices, sperm counts and sperm motility and the lack of histopathological findings for the testis and epididymis in these groups. Hence, a NOAEL for male and female fertility of 15,000 ppm (1016-1375 mg/kg body weight/day) can be derived on the basis of this study.

With respect to developmental effects, a delayed ear unfolding or eye opening was seen in F1 pups at the highest dose tested (15,000 ppm corresponding to approximately 1016-1375 mg/kg body weight/day) (Fujii et al. 2005). This finding was likely associated with the decreased F1 and F2 pup weight observed pre-weaning. Since pup weight was not affected at birth, lactational exposure to DEP may have exerted the reduction in pup weight. At the time of sexual maturation assessment, no difference in body weight was observed among the treatment groups. Still, a delayed female vaginal opening was seen at 15,000 ppm in the F1 rats. Overall, the NOAEL for developmental effects is considered 3000 ppm DEP (corresponding approximately to 197-267 mg/kg body weight/day).

Embryo-fetal development studies performed in mice and rats have shown reduced pup weight at birth, a reduced number of pups per litter and an increased frequency of skeletal variations at and above maternotoxic doses (Lamb et al. 1987; Field et al. 1993; Tanaka et al. 1987).

Clinical studies indicate an association between the level of the DEP metabolite MEP in prenatal maternal urine samples and reduced anogenital distance (an indicator of fetal androgen exposure) in male newborns (Swan et al. 2005, 2008). However, this finding was not confirmed in a recent Japanese study (Suzuki et al. 2012).

6.3. Polyvinyl acetate phthalate (PVAP)

There is very limited published scientific literature concerning the toxicity of PVAP (Schoneker et al. 2003). PVAP did not adversely affect reproductive function in rats at the highest dose tested (i.e., 1000

mg/kg body weight/day). Data from embryo-fetal development studies conducted in rats and rabbits showed that oral PVAP treatment resulted in reduced fetal weight and fetal abnormalities at 1000 mg/kg body weight/day in rats and 500 mg/kg body weight/day in rabbits, respectively. Since the nature of the fetal abnormalities was not specified in the publication, PVAP was not considered teratogenic. The findings made in rabbits occurred at a dose which also caused severe maternal toxicity but overall, the NOAELs for embryo-fetal developmental toxicity were 200 and 100 mg/kg body weight/day in rats and rabbits, respectively. In a pre- and postnatal development in rats, a decrease in the number of live pups was seen with a reported NOAEL of 200 mg/kg body weight/day.

6.4. Cellulose acetate phthalate (CAP)

There is very limited published scientific literature available concerning the toxicity of CAP (Hodge, 1944; Batt & Kotkoskie, 1999; Kotkoskie et al. 1999). The toxicity of CAP was evaluated in rodents in studies conducted with either CAP or CAP-based enteric coating material (i.e., an aqueous enteric coating material consisting of 67.9% CAP and minor amounts of distilled acetylated monoglycerides and poloxamer 188). In a GLP-compliant 90 day feeding study in rats, males receiving 50,000 ppm of the aqueous enteric coating material (equivalent to 3113 mg/kg body weight/day CAP) had statistically decreased absolute testicular weights. However, relative testicular weights (testes to brain weight ratios) were unaffected and no histological alterations were present that correlated with the decrease in absolute testes weight. Hence, the decrease in absolute testicular weights is not considered biologically relevant. Furthermore, there was no evidence of treatment-related maternal or embryo-fetal toxicity in a GLP-compliant embryo-fetal developmental toxicity study in which pregnant rats were fed up to 50,000 ppm of the aqueous enteric coating material in the diet on gestational days 6 to 15.

6.5. Hydroxypropyl methylcellulose acetate phthalate (HPMCP)

There is very limited published scientific literature available concerning the toxicity of HPMCP in general and reproductive and developmental toxicity of HPMCP in particular. In rats administered HPMCP orally via gavage, histopathology and organ weight evaluations revealed no effect on the reproductive organs following repeat-dosing of up to 6 g/kg body weight/day HPMCP for 6 months (Kitagawa et al. 1973).

7. Conclusion

This document provides specific recommendations on the use of the phthalates DBP, DEP and PVAP as excipients in human medicinal products. Data currently available for the phthalates CAP and HPMCP do not indicate that their presence of in human medicinal products constitutes a potential risk for human safety.

Adverse reproductive and/or developmental effects have been observed in non-clinical studies conducted with DBP, DEP or PVAP. Due to the lack of pharmacokinetic exposure data in humans and rats for these excipients, it can presently not be excluded that the findings made are of clinical relevance. As a result, Permitted Daily Exposure (PDE) values are established for DBP, DEP or PVAP based on the approach described in Appendix 3 of the ICH Q3C (R4) guideline.

While no effect on reproduction was observed, dietary administration of DEP was associated with developmental effects in an extended GLP-compliant two-generation reproductive toxicity study in rats (Fujii et al. 2005). Based on this study, a PDE for reproductive and developmental toxicity of 4 mg/kg body weight/day can be established for DEP based on a NOAEL of 197 mg/kg and uncertainty factors of 5 for interspecies variation (rat) and 10 for intraspecies variation. Hence, the daily DEP exposure resulting from administration of medicinal products should not exceed the PDE of 4 mg/kg/day.

Based on an increased incidence of fetal abnormalities at non-maternotoxic doses in a rat embryo-fetal toxicity study, a PDE for PVAP of 2 mg/kg body weight/day can be established applying uncertainty factors of 5 for interspecies variation (rat), 10 for intraspecies variation and an additional safety factor of 2 in order to compensate for that dosing was terminated already at gestation day 14. As a consequence, the PVAP content in human medicinal products should maximally give rise to a daily exposure corresponding to the PDE of 2 mg/kg/day

Based on findings of disturbed reproductive development in male rats described by Lee and co-workers (2004), a PDE for DBP of 0.01 mg/kg body weight/day can be established. The PDE calculation is based on a LOAEL of 2 mg/kg body weight/day and uncertainty factors of 5 for interspecies variation (rat), 10 for intraspecies variation and 4 since a NOAEL was not determined. The PDE is in line with the tolerable daily intake (TDI) for DBP of 0.01 mg/kg body weight which has been established by EFSA on basis of the findings described in the article by Lee et al. (2004). The amount of DBP in medicinal products should be reduced to a level corresponding to the PDE of 0.01 mg/kg/day.

Recommendations

The recommendations of this guideline should be considered as precautionary measures in the absence of clinical evidence on phthalate-induced adverse effects in humans.

It is expected that new medicinal products in applications for marketing authorisation will be in compliance with this guideline.

For existing authorised medicinal products, it is proposed to set 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.

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 and the presence or not of alternative treatment options. For instance, in severe or terminal disease conditions, the strict application of the PDE is not considered necessary for DBP, DEP or PVAP-containing medicinal products where the risk of reproductive and developmental toxicity is outweighed by the benefits of treatment for patients.

Additionally, the EMA will propose 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)”.

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