Background: Phthalates are synthetic chemical esters of phthalic acid, that are broadly divided into low molecular weight (LMW) phthalates, which include the likes of dibutyl phthalate (DBP), diethyl phthalate (DEP) and dimethyl phthalate (DMP); high molecular weight (HMW) phthalates, which encompass butylbenzyl phthalate (BBzP), di-2-ethylhexyl phthalate (DEHP), di-isodecyl phthalate (DiDP), di-isononyl phthalate (DiNP) and di-n-octyl phthalate (DnOP); and phthalate polymers, such as cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP) and polyvinyl acetate phthalate (PVAP). They confer numerous properties, including those as a lubricant, a solvent, a softener and a plasticizer, which increases flexibility and durability. Consequently they were once widely found in a variety of consumer products, thus leading to ubiquitous daily exposure [1].

However, concerns have been raised regarding the effects of certain phthalates on reproduction and development. These worries predominantly stem from their endocrine-disrupting properties, and associated anti-androgen implications. They have been well documented pre-clinically, particularly in the rat, where prenatal exposure to particular phthalates has affected male and female offspring, with respect to numerous parameters including anogenital distance (AGD), gender ratio, nipple retention, ear and eye unfolding, vaginal opening and foetal weight and viability [2–4]. In addition, it has been demonstrated that their
effects are additive when combined with each other, as well as, different classes of anti-androgen chemicals [5]. In fact the endocrine-disrupting effects of phthalates in the rat are so robust that within endocrinology laboratories, phthalates are often used as tools to induce testicular dysgenesis syndrome (TDS). By contrast to the preclinical arena, where there are vast studies evaluating the health implications of phthalates, too many to discuss within the scope of this article, clinical data are few and far between. Those that exist come from human association studies and suggest that prenatal exposure to certain phthalates reduces the AGD amongst male offspring, possibly indicative that it compromises virilisation [6, 7]. There is also evidence to suggest that prenatal exposure reduces masculine-play behaviour amongst pre-school males [8]. Furthermore, evaluation of phthalate exposure during adulthood demonstrates that it may contribute to both a reduction in the levels of circulating steroid hormones and sperm quality in males, as well as reduced fertility, in both males and females [9–12].

Whilst it is acknowledged that clinical data are limited and, in some cases inconsistent, regulatory bodies affiliated with consumer goods that contain phthalates deemed it necessary to take precautionary measures. Consequently, guidelines have been developed aimed at reducing exposure to certain phthalates in cosmetics [13], childcare articles [14], plastics in contact with food [15] and medical devices [16–18]. Certain medicines represent a source of phthalate exposure, where they exist as excipients, that is, inactive components. Since phthalates are insoluble in acidic environments and soluble in neutral and alkaline conditions, they are commonly used as plasticizing agents in gastrointestinal-resistant film coatings for tablets, capsules, beads and granules, thus enabling targeted delivery of active ingredient(s) to the more alkaline environment of the intestine. This is likely the reason that drugs for gastrointestinal indications have been identified as particularly high sources of phthalate exposure [19, 20]. Furthermore, animal and human pharmacokinetic studies have shown that LMW phthalates, such as DBP and DEP, have near complete intestinal absorption, with 78–90 % of the administered dose excreted in the urine within 24 h [21–23]. However, for the HMW phthalates CAP, PVAP and HPMCP, there is currently no pharmacokinetic data available.

Accordingly in 2012, the Food and Drug Administration (FDA) also developed guidelines aimed at minimising phthalate exposure in products regulated by the Centre for Drug Evaluation and Research (CDER) [24]. Specifically, the Agency determined that there is evidence that exposure to DBP and DEHP from pharmaceuticals presents a potential risk of developmental and reproductive toxicity. While the Agency recognised that drug products may carry inherent risks, it stated that DBP and DEHP are used as excipients, and safer alternatives are available. Therefore, the Agency recommends that DBP and DEHP be avoided as excipients in CDER-regulated drug and biologic products [24]. In line with the FDA, the EMA’s Committee for Medicinal Products for Human Use (CHMP) is currently drafting its own recommendations on the use of phthalates as excipients in human medicinal products [1]. Whilst these guidelines have yet to be finalised, they are expected to propose permitted daily exposures (PDE) of ≤ 0.01, 4 and 2 mg/kg for DBP, DEP and PVAP, respectively and are predicted to be enforced in 2015. For existing authorised medicinal products, the EMA is proposing to set a time limit of three years (after coming into force of the final guideline) for the implementation of formulation changes and consequential regulatory applications, as necessary. Ahead of their implementation, the authors of this study aimed to identify which United Kingdom (UK)-licensed drugs are likely to be affected by the proposed EMA guidelines, in order to help prepare for potential consequences.

Methods

The first step in this process was to identify which UK licensed medicines contain at least one of the three precautionary phthalates, DBP, DEP and PVAP, named in the draft EMA guidelines. The electronic Medicines Compendium (eMC) [25] was deemed an effective way to find these medicines, as it contains up to date information about most medicines licensed in the UK and is checked and approved by either the Medicines and Healthcare products Regulatory Agency (MHRA) or the EMA. The eMC was utilised via the algorithm depicted in Fig. 1.

The eMC provided the medical information email address associated with each medicine found to contain the precautionary phthalates. The next stage was to contact the companies affiliated with each of the medicines identified as containing the precautionary phthalates. In many cases, a single medical information address was affiliated with numerous products, thus it was only necessary to issue emails to 28 different medical information companies, requesting information about the maximum daily exposure of the relevant phthalate(s) in their product(s). Twenty-seven companies were contacted using the medical information email address provided by the eMC and one was contacted by an online enquiry form. The companies were made aware of the proposed EMA guidelines and their phthalate containing product(s) was identified together with a request for information on the maximum daily exposure of the affiliated phthalate(s).

Results

The eMC search to identify UK medicines containing at least one of the three precautionary phthalates, DBP, DEP and PVAP, named in the draft EMA guidelines, produced 50 hits (information correct as of 9th June 2014), one of which was deemed a false positive because the drug was
listed as discontinued (Maxolon SR 15 mg Capsules). The remaining 49 hits, consisted of 54 branded medicines, five of which contained DBP alone, 17 contained DEP alone, 27 contained PVAP alone, four contained DEP in combination with PVAP and one contained DBP in combination with DEP (Table 1). It should be noted that this list will only contain those drugs registered on the eMC.

Whilst some companies provided maximum daily exposure as requested, thus enabling direct comparison with those set out in the draft guidelines, others did not specify exposure levels but instead commented on how exposure compared with the guidelines. In some instances, companies stipulated the amount of phthalate present in a single unit of the medicine, thus requiring the authors to calculate the maximum daily exposure based on maximum indicated dose as per the ‘summary of product characteristics’ (SPC). There were five cases where companies stated that they were unable to quantify (UTQ) exposure and for 11 products, companies refused to declare (RTD). Remaining companies provided no response (NR) at all which amounted to 12 products. Responses are summarised in Table 1, however, we were unable to include the phthalate content for 23 products because either the licence holder refused to declare or provided no response.

The proposed permitted daily exposures (PDE) in the EMA guidance equates to < 0.7 mg for DBP, 280 mg for DEP and 140 mg for PVAP, for an individual with 70 kg body weight. Where the licence holder supplied information regarding DBP content, the level was above the proposed EMA PDE of 0.7 mg for 70 kg body weight in Asacol 800 mg MR (Warner Chilcott UK Ltd) and Vivotif (Crucell Italy S.r.l), the levels being 48 mg and 8 mg, respectively, at the maximum licensed daily dose.

Phthalate in tablet/capsule/liquid formulation
Where the phthalate was contained as an excipient within the dosage form, the level of phthalate varied considerably. The EMA proposes that the presence in medicinal products of DBP, DEP or PVAP at levels giving rise to daily exposures above the PDEs may 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. Furthermore, the EMA also proposes that in severe or terminal disease conditions, the strict application of the PDE may not be 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.

Consequently, the drugs were assessed in terms of whether or not they are used acutely or chronically. Where a drug may be used in either an acute or a chronic condition, it was categorised as “chronic”, due to the possibility that the drug may be prescribed on a long-term basis. Drugs were also categorised according to whether or not they are licensed for use in pregnancy. The SPC for some drugs advises caution in pregnancy or the drug may be used where the benefit outweighs the risk. For both of these categories, drugs were described as “benefit > risk” (Table 1).

Where the licence holder supplied information regarding DEP content, the level was above the proposed EMA PDE of 0.7 mg for 70 kg body weight in Asacol 800 mg MR (Warner Chilcott UK Ltd) and Vivotif (Crucell Italy S.r.l), the levels being 48 mg and 8 mg, respectively, at the maximum daily dose.

Phthalate in tablet/capsule logo ink
For some preparations, the phthalate was contained in the tablet/capsule logo ink on the surface of the dosage formulation. In all of these preparations, the phthalate was PVAP. For those companies who responded, the level of PVAP in the ink in each preparation was below proposed EMA PDE in all products. In some cases, the manufacturer declared that the phthalate content was so low per dosage form that it was negligible or too low to measure accurately.
| Trade Name (generic name) | License holder | Phthalate Phthalate content (mg) per tablet/capsule | Maximum licensed daily dose of drug | Phthalate (mg) at maximum daily dose | Chronic/ Acute Use in pregnancy |
|--------------------------|----------------|--------------------------------------------------|----------------------------------|----------------------------------|-------------------------------|
| Asacol 800 mg MR Tablets (mesalazine) | Warner Chilcott UK Ltd | DBP 8.00 | 4.8 mg | 48.00 | Chronic Benefit>Risk |
| Coracten XL 30 mg (Nifedipine) | UCB Pharma Ltd | DBP 0.14 | 90 mg | 0.42 | Chronic No |
| Coracten XL 60 mg (Nifedipine) | UCB Pharma Ltd | DBP 0.28 | 90 mg | 0.28 | Chronic No |
| Occlusal (Salicylic acid) | Alliance Pharmaceuticals | DBP N/A | RTD | RTD | Chronic No |
| Timodine Cream (Nystatin, Dimeticone, Hydrocortisone & Benzalkonium Chloride) | Alliance Pharmaceuticals | DBP N/A | RTD | RTD | Chronic No |
| Vivofit (Salmonella enterica serovar Typhi) | Crucell Italy S.r.l | DBP / DEP 8.00 / 8.00 | 1 tablet | 8.00 / 8.00 | Chronic No |
| Kenzem 120 mg SR Capsules (Diltiazem hydrochloride) | Kent Pharmaceuticals | DEP NR | 480 mg | NR | Chronic No |
| Kenzem 90 mg SR Capsules (Diltiazem hydrochloride) | Kent Pharmaceuticals | DEP NR | 480 mg | NR | Chronic No |
| Kenzem 60 mg SR Capsules (Diltiazem hydrochloride) | Kent Pharmaceuticals | DEP NR | 480 mg | NR | Chronic No |
| Omeprazole 40 mg Gastro-resistant Capsules, Hard (Omeprazole) | Accord Healthcare Ltd | DEP 0.15 | 120 mg | 0.45 | Chronic Yes |
| Omeprazole 20 mg Gastro-resistant Capsules, Hard (Omeprazole) | Accord Healthcare Ltd | DEP 0.15 | 120 mg | 0.90 | Chronic Yes |
| Reminyl XL 24 mg Prolonged Release Capsules (Galantamine) | Shire Pharmaceuticals Ltd | DEP NR | 24 mg | NR | Chronic Benefit>Risk |
| Reminyl XL 16 mg Prolonged Release Capsules (Galantamine) | Shire Pharmaceuticals Ltd | DEP NR | 24 mg | NR | Chronic Benefit>Risk |
| Reminyl XL 8 mg Prolonged Release Capsules (Galantamine) | Shire Pharmaceuticals Ltd | DEP NR | 24 mg | NR | Chronic Benefit>Risk |
| Rheumatac Retard 75 mg Tablets (Diclofenac sodium) | Adipharm Mercury Company Ltd | DEP 0.95 | 150 mg | 1.90 | Chronic No |
| Surgical Spirit BP (Virgin castor oil & Methyl salicylate) | Thornton & Ross Ltd | DEP N/A | N/A | UTQ | Chronic Benefit>Risk |
| Videx EC 400 mg Gastro-resistant Capsules (Didanosine) | Bristol-Myers Squibb Pharmaceuticals Ltd | DEP RTD | 400 mg | RTD | Chronic Benefit>Risk |
| Videx EC 250 mg Gastro-resistant Capsules (Didanosine) | Bristol-Myers Squibb Pharmaceuticals Ltd | DEP RTD | 400 mg | RTD | Chronic Benefit>Risk |
| Videx EC 200 mg Gastro-resistant Capsules (Didanosine) | Bristol-Myers Squibb Pharmaceuticals Ltd | DEP RTD | 400 mg | RTD | Chronic Benefit>Risk |
| Videx EC 125 mg Gastro-resistant Capsules (Didanosine) | Bristol-Myers Squibb Pharmaceuticals Ltd | DEP RTD | 400 mg | RTD | Chronic Benefit>Risk |
| Volsaid Retard 100 mg Tablets (Diclofenac Sodium) | Chiesi Ltd | DEP 1.27 | 100 mg | 1.27 | Chronic No |
| Medicine                                                                 | Manufacturer                        | Phthalate | Maximum Daily Exposure | Benefit:Risk |
|------------------------------------------------------------------------|-------------------------------------|-----------|------------------------|--------------|
| **Table 1 UK licensed medicines that contain DBP, DEP and/or PVAP and respective maximum daily exposures relative to proposed EMA guidelines (Continued)** |
| Volsaid Retard 75 mg Tablets (Diclofenac Sodium)                        | Chiesi Ltd                          | DEP       | 0.95                   | 150 mg       | 1.90          | Acute | No |
| Boots Constipation Relief Tablets 40s (Bisacodyl)                      | Dr. Reddy’s Laboratories (UK) Ltd   | DEP       | NR                     | 2 tablets    | NR            | Acute | No |
| Epilim 500 Gastro-resistant Tablets (Sodium valproate)                 | Sanofi                              | DEP / PVAP| 2.31 / 23.31           | 2500 mg      | 11.55 / 116.55 | Chronic | No |
| Epilim 200 Gastro-resistant Tablets (Sodium valproate)                 | Sanofi                              | DEP / PVAP| 1.23 / 12.43           | 2500 mg      | 14.76 / 149.16 | Chronic | No |
| Zentiva 500 mg Gastro-resistant Tablets (Sodium valproate)             | Winthrop Pharmaceuticals UK Ltd     | DEP / PVAP| 2.31 / 23.31           | 2500 mg      | 11.55 / 116.55 | Chronic | No |
| Zentiva 200 mg Gastro-resistant Tablets (Sodium valproate)             | Winthrop Pharmaceuticals UK Ltd     | DEP / PVAP| 1.23 / 12.43           | 2500 mg      | 14.76 / 149.16 | Chronic | No |
| Boots Alternatives Laxative Tablets (Senna, Aloin, Cascara bark extract) | G.R. Lane Health Products Ltd       | PVAP      | 2.10                   | 2 tablets    | 4.20          | Acute | No |
| Boots Period Pain Relief 250 mg Gastro-resistant Tablets (Naproxen)     | Teva UK Ltd                         | PVAP      | NR                     | 500 mg       | NR            | Acute | No |
| Deltacortril 2.5 mg Gastro-resistant Tablets (Prednisolone)             | Alliance Pharmaceuticals             | PVAP      | RTD                    | 60 mg        | RTD           | Chronic | Benefit>Risk |
| Deltacortril 5 mg Gastro-resistant Tablets (Prednisolone)               | Alliance Pharmaceuticals             | PVAP      | RTD                    | 60 mg        | RTD           | Chronic | Benefit>Risk |
| Disipal 50 mg Tablets (Orphenadrine hydrochloride)                     | Astellas Pharma Ltd                 | PVAP      | 17.30                  | 400 mg       | 138.40        | Chronic | Benefit>Risk |
| Feminax Ultra 250 mg Gastro-resistant Tablets (Naproxen)                | Teva UK Ltd                         | PVAP      | NR                     | 750 mg       | NR            | Acute | No |
| Ferrous Gluconate 300 mg Tablets (Ferrous gluconate)                   | Kent Pharmaceuticals                 | PVAP      | NR                     | 1800 mg      | NR            | Chronic | Yes |
| Nardil 15 mg Tablets (Phenelzine)                                      | Archimedes Pharma UK Ltd            | PVAP      | 1.42                   | 90 mg        | 8.52          | Chronic | No |
| Prednisolone 5 mg Gastro-resistant Tablets (Prednisolone)              | Actavis UK Ltd                      | PVAP      | 12.00                  | 60 mg        | 144.00        | Chronic | Benefit>Risk |
| Prednisolone 2.5 mg Gastro-resistant Tablets (Prednisolone)             | Actavis UK Ltd                      | PVAP      | 12.00                  | 60 mg        | 288.00        | Chronic | Benefit>Risk |
| Pancex Granules (Pancreatin)                                           | Essential Pharmaceuticals Ltd        | PVAP      | variable              | RTD          | Chronic       | Benefit>Risk |
| Pancex V Tablets (Pancreatin)                                          | Essential Pharmaceuticals Ltd        | PVAP      | variable              | RTD          | Chronic       | Benefit>Risk |
| Pancex V Forte Tablets (Pancreatin)                                    | Essential Pharmaceuticals Ltd        | PVAP      | variable              | RTD          | Chronic       | Benefit>Risk |
| Phthalate in tablet/capsule logo ink                                   | Sinclair IS Pharma                  | PVAP      | UTQ                   | 500 µg       | UTQ           | Acute | No |
| Amitiza 24 µg Soft Capsules (Lubiprostone)                             | Sucampo Pharma Europe Ltd           | PVAP      | 0.21                  | 48 µg        | 0.42          | Acute | No |
| Medicine                                      | Manufacturer                        | PVAP | Maximum Daily Exposure | Maximum Daily Exposure | Acute | Benefit/Risk |
|-----------------------------------------------|-------------------------------------|------|------------------------|------------------------|-------|--------------|
| Anadin Ultra Double Strength/LiquiFast 400 mg Capsules (Aspirin)          | Pfizer Consumer Healthcare          | <0.01 | 1200 mg                | 0.03                   | Acute | No           |
| Anadin Ultra/LiquiFast 200 mg Capsules (Aspirin)                           | Pfizer Consumer Healthcare          | <0.01 | 1200 mg                | 0.05                   | Acute | No           |
| Aptivus 250 mg soft Capsules (Tipranavir)                                     | Boehringer Ingelheim Ltd            | UTQ  | 1000 mg                | UTQ                    | Chronic | Benefit>Risk |
| Benadryl Allergy Liquid Release 10 mg Capsules (Cetirizine dihydrochloride) | McNeil Products Ltd                 | 1.00 | 10 mg                  | 1                      | Chronic | Benefit>Risk |
| Nurofen Express 200 mg Liquid Capsules (Ibuprofen)                          | Reckitt Benckiser Healthcare (UK) Ltd | NR   | 1200 mg                | NR                     | Acute | No           |
| Nurofen Express 400 mg Liquid Capsules (Ibuprofen)                          | Reckitt Benckiser Healthcare (UK) Ltd | NR   | 1200 mg                | NR                     | Acute | No           |
| Targretin 75 mg Capsules (Bexarotene)                                         | Eisai Ltd                           | UTQ  | 21 capsules            | UTQ                    | Acute | No           |
| Xtandi 40 mg Soft Capsules (Enzalutamide)                                    | Astellas Pharma Ltd                 | UTQ  | 160 mg                 | UTQ                    | Acute | No           |
| Zemplar Soft Capsules 2 µg (Paricalcitol)                                    | AbbVie Ltd                          | 0.86 | 32 µg                  | 13.76                  | Chronic | Benefit>Risk |
| Zemplar Soft Capsules 1 µg (Paricalcitol)                                    | AbbVie Ltd                          | 0.86 | 32 µg                  | 27.52                  | Chronic | Benefit>Risk |

All calculations are based on the maximum licensed dose. If a drug has multiple indications, the indication with the highest dose was used for the calculation. For drugs that cannot be given at the maximum dose due to their dose increment, i.e. sodium valproate 200 mg – max dose 2500 mg, the maximum achievable dose within the product license was used.

UTQ denotes unable to quantify, RTD denotes licence holder refused to declare, NR denotes no response

a Dosing regime of Pancrex is dependent on frequency of meals/snacks
b Based on a dose of 650 mg/m²/day for a person with a body surface area of 2.38–2.62 m²
c Information in the public domain [26, 27], license holder refused to confirm
d These medications are also used in acute settings
(Sanofi) and Zentiva 200 mg Gastro-resistant Tablets (Winthrop Pharmaceuticals UK Limited) contained a level of PVAP that was above the EMA PDE. The PVAP level was 149.16 μg in both sodium valproate 200 mg formulations.

Discussion

Summary

The aim of this study was to identify which UK licensed medicines are likely to be affected by proposed EMA guidelines on the use of phthalates as excipients in human medicinal products. Although we attempted to identify as many phthalate-containing preparations as possible by reviewing SPCs, this list cannot be considered exhaustive. For 23 products, the licence holder refused to declare the phthalate content or gave no response. At face value, it appeared that many medicines would be impacted by the recommendations as 54 medicines were identified as containing the precautionary phthalates DBP, DEP and PVAP, named in the guidelines. However, for those medicines where companies responded, once maximum daily phthalate exposures were established, only six branded medicines, namely Asacol 800 mg MR (Warner Chilcott UK Ltd), Epilim 200 Gastro-resistant Tablets (Sanofi), Prednisolone 2.5 and 5 mg Gastro-resistant Tablets (Actavis UK Ltd), Vivitof (Crucell Italy S.r.l.), and Zentiva 200 mg Gastro-resistant Table (Winthrop Pharmaceuticals UK Limited), were identified as exceeding the EMA’s proposed recommendations. Thus, this study will help to appease those concerned about the implications of enforcement of these guidelines.

Strengths and limitations

To the authors’ knowledge, this study has provided the first review of the presence of phthalates in UK licenced medications. Furthermore, it has identified, where possible, which phthalate-containing medications will be affected by EMA guidance once it comes into practice. By virtue of the limited information in the public domain and the proprietary nature of drug formulations, information on the concentration of phthalates was limited to only 57 % of the drugs identified. This highlights the potential difficulty in clinical practice when undertaking a risk/benefit approach in the preceding 3 years before the enforcement of this guidance. In addition, not all SPCs are available on the eMC, further hindering the ability of making an informed decision in certain patient populations.

Conclusion

For those medicines identified as exceeding the EMA’s recommendations, this study has highlighted the need to instigate a risk-benefit review, particularly in patients of childbearing age and/or with chronic conditions. To facilitate this process, the EMA suggests taking into account factors such as the presence of non-phthalate containing alternatives, the intended patient population and the severity of the disease being treated.

Abbreviations

AGD: Anogenital distance; BBzP: Butylbenzyl phthalate; CAP: Cellulose acetate phthalate; CDER: Centre for Drug Evaluation and Research; DBP: Dibutyl phthalate; DEHP: Di-2-ethylhexyl phthalate; DEP: Diethyl phthalate; DnOP: Di-n-octyl phthalate; EMA: European Medicines Agency; eMC: Electronic medicines compendium; FDA: Food and Drug Administration; HMW: High molecular weight; HPMCP: Hydroxypropyl cellulose-phthalate; LMW: Low molecular weight; MHRA: Medicines and Healthcare products Regulatory Agency; NR: No response; PDE: Permitted daily exposure; PVAP: Polyvinylacetate phthalate; RTD: Refused to declare; SPC: Summary of product characteristics; TDS: Testicular dysgenesis syndrome; UTQ: Unable to quantify.

Competing Interests

Lisa Jamieson has served as a consultant for Tillotts Pharma UK Ltd and has received research funding from Tillotts Pharma UK Ltd. William McCully is an employee of Tillotts Pharma UK Ltd.

Authors’ contributions

Li carried out the research of this study and assisted in the production of the manuscript. WM conceived of the study, participated in its research and assisted in the production of the manuscript. All authors read and approved the final manuscript.

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Author details

1Enucleo Limited, Farharn, Surrey, UK. 2Tillotts Pharma UK Ltd., Larbourne Suite, 8 The Stables, Wellington, Wellington, Lincoln LNS 0HX, UK.

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