
Guidance for Industry Limiting the Use of Certain Phthalates as Excipients in CDER-Regulated Products

DRAFT GUIDANCE

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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**March 2012
CMC**

Guidance for Industry

Limiting the Use of Certain Phthalates as Excipients in CDER-Regulated Products

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1 **Guidance for Industry¹**
2 **Limiting the Use of Certain Phthalates as Excipients in CDER-**
3 **Regulated Products**
4

5
6 This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current
7 thinking on this topic. It does not create or confer any rights for or on any person and does not operate to
8 bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of
9 the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA
10 staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call
11 the appropriate number listed on the title page of this guidance.
12

13
14
15 **I. INTRODUCTION**
16

17 This draft guidance provides the pharmaceutical industry with the Center for Drug Evaluation
18 and Research's (CDER's) current thinking on the potential human health risks associated with
19 exposure to dibutyl phthalate (DBP) and di(2-ethylhexyl) phthalate (DEHP). In particular, the
20 draft guidance recommends that the pharmaceutical industry avoid the use of these two specific
21 phthalates as excipients in CDER-regulated drug and biologic products, including prescription
22 and nonprescription products.
23

24 The recommendations in this guidance do not address the use of DBP or DEHP in other types of
25 FDA-regulated products or exposure to DBP or DEHP due to the presence of any of these
26 compounds as an impurity—including as a result of leaching from packaging materials.
27

28 FDA's guidance documents, including this guidance, do not establish legally enforceable
29 responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should
30 be viewed as recommendations, unless specific regulatory or statutory requirements are cited.
31 The use of the word *should* in Agency guidances means that something is suggested or
32 recommended, but not required.
33

34 **II. BACKGROUND**
35

36 Phthalate esters (phthalates) are synthetic chemicals with a broad spectrum of uses. Phthalates
37 are found in certain pharmaceutical formulations, primarily as a plasticizer in enteric-coatings of
38 solid oral drug products to maintain flexibility, but they also may be used for different functions
39 in other dosage forms. Phthalates also are found in other products for uses such as softeners of
40 plastics, solvents in perfumes, and additives to nail polish, as well as in lubricants and insect
41 repellents.

¹ This guidance has been prepared by the Office of Pharmaceutical Science, Office of New Drugs, Office of Compliance, and Office of Regulatory Policy in the Center for Drug Evaluation and Research at the Food and Drug Administration.

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42 Phthalates have been studied extensively in animals, and some phthalates have demonstrated no
43 appreciable toxicity. Certain phthalates, however, have been shown to be developmental and
44 reproductive toxicants in laboratory animals. These phthalates are endocrine-disrupting
45 chemicals in animals and may interfere with the production, secretion, transportation,
46 metabolism, receptor binding, mediation of effects, and excretion of natural hormones that
47 regulate developmental processes and support endocrine homeostasis in the organism. These
48 same phthalates are suspected of being endocrine-disrupting in humans, and effects would
49 depend on the systemic exposure (Jurewicz and Hanke 2011).

50
51 Data from the National Health and Nutrition Examination Survey (NHANES) indicate
52 widespread exposure of the general population to phthalates (CDC 2009). Humans are exposed
53 to phthalates by multiple routes, including inhalation, ingestion, and to a lesser degree absorption
54 through the skin. Several observational human studies have reported an association between
55 exposure to certain phthalates and adverse developmental and reproductive effects. The
56 ubiquitous presence of phthalates in the environment and the potential consequences of human
57 exposure to phthalates have raised concerns, particularly in vulnerable populations such as
58 pregnant women and infants.

59 A number of regulatory authorities have begun taking steps to more closely regulate certain
60 phthalates. For example:

- 61 • Congress has prohibited the use of DBP, DEHP, and another phthalate—butyl benzyl
62 phthalate (BBP)—in children’s toys at concentrations higher than 0.1 percent (Consumer
63 Product Safety Improvement Act 2008).
- 64 • The European Commission identified DBP, DEHP, and BBP as reproductive toxicants
65 (Directive 2005/84/EC), and the European Union prohibits their use as ingredients in
66 cosmetics (Directive 2005/90/EC).
- 67 • The Environmental Protection Agency (EPA) added certain phthalates, including DBP
68 and DEHP, to the list of chemicals of concern under the Toxic Substances Control Act
69 and included them in the Toxics Release Inventory list (EPA 2009).
- 70 • FDA’s Center for Devices and Radiological Health issued recommendations regarding
71 minimizing exposure to PVC devices containing DEHP and provided recommendations
72 for high-risk procedures (CDRH “DEHP in Plastic Medical Devices”).

73
74 Of the phthalates for which significant concern has been expressed because of their reproductive
75 and developmental toxicity, only DBP and DEHP have been used in CDER-regulated drug or
76 biologic products. The recommendations in this guidance apply only to DBP and DEHP.

77 78 **III. DISCUSSION**

79
80 Phthalates have been studied extensively in animals, and DBP and DEHP have been shown to be
81 developmental and reproductive toxicants in laboratory animals. While the data in humans are
82 less clear, epidemiological studies suggest that certain phthalates may affect reproductive and
83 developmental outcomes. Other studies have confirmed the presence of DBP and DEHP in
84 amniotic fluid, breast milk, urine, and serum.

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85 **A. NONCLINICAL STUDIES**

86
87 Phthalates generally have low acute toxicity in animals. However, repeated exposure to certain
88 phthalates, including DBP and DEHP, in animals has been associated with various adverse
89 effects—notably the disruption of the development of the male reproductive system.
90

91 *Dibutyl Phthalate (DBP)*

92 Exposure to DBP has been shown to cause decreased sperm counts in male animals and reduced
93 fertility in both female and male animals. Exposure in pregnant animals has resulted in fetal
94 skeletal malformations and decreased anogenital distance in the male offspring. Adverse effects
95 on the male reproductive system have been seen in several species, including rats, mice, and
96 guinea pigs (EPA 2006; Lehman et al. 2004). Male rats exposed directly to DBP for short
97 periods of time at different stages of development also have shown abnormalities in reproductive
98 development/function, including testicular atrophy and decreased spermatocytes and
99 spermatogonia (Gray and Gangolli 1986; Cater et al. 1977). Some of these studies have
100 indicated that adverse effects on male reproductive function can be seen in rats following a
101 relatively short period of exposure to DBP.
102

103 Other studies in rodents have suggested that DBP may impair fertility in exposed females
104 (Lehman et al. 2004). Finally, high doses of DBP have been associated with developmental
105 abnormalities in rats, including skeletal abnormalities such as fusion or absence of cervical
106 vertebral arches and fetal malformations such as cleft palate (Ema, Amano, and Ogawa 1994;
107 Ema et al. 1995; Ema et al. 1993). Based on the adverse effects in animals, the EPA-
108 recommended oral Reference Dose (RfD)² for DBP is 0.1 mg/kg/day.
109

110 *Di(2-ethylhexyl) Phthalate (DEHP)*

111 Exposure to DEHP has shown similar adverse effects as DBP on the male reproductive system.
112 In a multigeneration continuous breeding study, exposure of female rats to DEHP resulted in F1
113 and F2 nonbreeding adult males with small or absent reproductive organs (NTP-CERHR 2005).
114 In another study, female rats administered DEHP from gestation day 6 through lactation day 21
115 had male pups with nipple retention and reduced anogenital distance at a dose of 405 mg/kg/day,
116 and delayed preputial separation was seen at doses of 15 mg/kg/day and above (Andrade et al.
117 2006). Oral exposure to approximately 100-200 mg/kg/day of DEHP during gestation resulted in
118 skeletal and cardiovascular malformations, neural tube defects, developmental delays, and
119 intrauterine death of the offspring. Based on these adverse effects in animals, the EPA-
120 recommended RfD for DEHP is 0.02 mg/kg/day.
121

122 **B. CLINICAL STUDIES**

123
124 There are limited data on the health effects of DBP and DEHP in humans. Several studies have
125 sought to quantify human exposure to phthalates using measurements of phthalate ester
126 metabolites in urine. Phthalates are metabolized and excreted quickly, so urinary levels of
127 phthalate ester metabolites reflect recent exposure to the parent diester. The Fourth National
128 Report on Human Exposure to Environmental Chemicals (CDC 2009) provides data on levels of

² The RfD is an estimate of a daily oral exposure to human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

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129 individual phthalate metabolites in the urine of several thousand participants who took part in the
130 NHANES during 2003-2004. Researchers found measurable levels of many phthalate
131 metabolites in the general population, indicating widespread exposure in the U.S. population to
132 phthalate esters, including DBP and DEHP.

133
134 Studies measuring phthalate ester metabolite levels in pregnant women, maternal and umbilical
135 cord plasma, and amniotic fluid samples have suggested that exposure to phthalates can occur in
136 utero (Silva et al. 2004; Huang et al. 2009). Available human lactation data also show breast
137 milk is a potential source of exposure to phthalate esters, including DBP and DEHP (Main et al.
138 2006).

139
140 Phthalate ester metabolites have been used as biomarkers to estimate exposure-related effects of
141 phthalate esters, but these studies are only able to indicate association, not causation. Several
142 such observational studies have shown an association between exposure to certain phthalates and
143 adverse reproductive outcomes and developmental effects similar to those found in animals. In
144 one study, maternal urinary concentrations of certain phthalate ester metabolites, including
145 monoethyl phthalate (MEP) and mono-n-butyl phthalate (MBP), were negatively related to
146 anogenital distance in newborn boys (Swan et al. 2005). Other studies evaluating the effects of
147 phthalate exposure on adult males found a dose-response relationship between MBP (Hauser et
148 al. 2006) with one or more semen parameters, including low sperm concentrations and motility.

149

150 **IV. RECOMMENDATIONS**

151

152 Although the current available human data are limited, the Agency has determined that there is
153 evidence that exposure to DBP and DEHP from pharmaceuticals presents a potential risk of
154 developmental and reproductive toxicity. While it is recognized that drug products may carry
155 inherent risks, DBP and DEHP are used as excipients, and safer alternatives are available.
156 Therefore, the Agency recommends avoiding the use of DBP and DEHP as excipients in CDER-
157 regulated drug and biologic products.

158

159 These recommendations apply to CDER-regulated drug and biologic products that are under
160 development (i.e., investigational new drugs (INDs)), nonapplication products (e.g., over the
161 counter (OTC) monograph products), and both marketed approved products and those currently
162 under review for marketing consideration (i.e., new drug applications (NDAs), abbreviated new
163 drug applications (ANDAs), and biologics license applications (BLAs)).

164

165 There are alternatives to DBP and DEHP for use as excipients in CDER-regulated products.
166 Manufacturers with products that contain DBP or DEHP should consider alternative excipients
167 and determine if the alternative excipient they plan to use has been used in similar CDER-
168 approved products and at what level. The Inactive Ingredients Database provides information on
169 excipients present in FDA-approved drug products, and this information can be helpful in
170 developing drug products.³

³ As manufacturers reformulate their products, the listings for dibutyl phthalate (DBP) and di(2-ethylhexyl) phthalate (DEHP) will be removed from the Inactive Ingredients Database (www.accessdata.fda.gov/scripts/cder/iig/index.cfm).

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171 For any currently marketed formulation that includes DBP or DEHP, the applicable Scale-up and
172 Post-Approval Changes (SUPAC) guidances should be referenced to determine the level of
173 change to the formulation and the information (e.g., bridging studies) that should be submitted to
174 support the change. (See, for example, SUPAC guidances for industry on Modified Release
175 Solid Oral Dosage Forms (SUPAC-MR, September 1997); Nonsterile Semisolid Dosage Forms
176 (SUPAC-SS, May 1997); and Immediate Release Solid Oral Dosage Forms (SUPAC-IR,
177 November 1995).) The scientific thinking provided in the appropriate guidances also can be
178 used for those products currently under development that may include DBP or DEHP. While the
179 Inactive Ingredient Database lists the levels of excipients used in approved products per dosage
180 form, manufacturers should take into account the total daily exposure at the maximal use
181 conditions and contact the appropriate CDER review division to determine what studies
182 supporting the use of the alternative excipient may be required. Additional studies also may be
183 required if a novel excipient is used.

184
185 Manufacturers of currently marketed products approved under an NDA or ANDA should refer to
186 the guidance for industry, *Changes to an Approved NDA or ANDA*, for information on the
187 reporting category associated with a change in excipient (FDA guidance for industry April
188 2004). Questions related to nonapplication drug products should be directed to the appropriate
189 CDER review division.

190
191 If a manufacturer determines that an alternative to DBP or DEHP cannot be used, the
192 manufacturer should provide justification for why DBP or DEHP should be used. Such
193 justification should include data to support why a safer alternative cannot be substituted, as well
194 as a risk/benefit analysis that demonstrates that the benefit for the intended population outweighs
195 potential safety concerns. The CMC information should be provided in Module 2 and Module 3
196 of a [common technical document \(CTD\) formatted application](#), while nonclinical studies
197 supporting the use of these phthalates in an application for a marketed drug product should be
198 provided in Module 4 of a [common technical document \(CTD\) formatted application](#).

199
200 A product marketed under an OTC monograph is generally recognized as safe and effective (and
201 not misbranded) if the product conforms to the monograph and contains only suitable inactive
202 ingredients that are safe in the amounts administered.⁴ The Agency generally does not consider
203 DBP or DEHP safe or suitable as an inactive ingredient in OTC monograph products.

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