

DEPARTMENT OF HEALTH AND HUMAN SERVICES**Food and Drug Administration**

[Docket No. FDA-2012-D-0108]

Draft Guidance for Industry on Limiting the Use of Certain Phthalates as Excipients in Center for Drug Evaluation and Research-Regulated Products; Availability**AGENCY:** Food and Drug Administration, HHS.**ACTION:** Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a draft guidance for industry entitled "Limiting the Use of Certain Phthalates as Excipients in CDER-Regulated Products." This draft guidance provides the pharmaceutical industry with the Center for Drug Evaluation and Research's (CDER's) current thinking on the potential human health risks associated with exposure to dibutyl phthalate (DBP) and di(2-ethylhexyl) phthalate (DEHP). In particular, the draft guidance recommends that the pharmaceutical industry avoid the use of these two specific phthalates as excipients in CDER-regulated drug and biologic products, including prescription and nonprescription products.

DATES: Although you can comment on any guidance at any time (see 21 CFR 10.115(g)(5)), to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance, submit either electronic or written comments on the draft guidance by May 31, 2012.

ADDRESSES: Submit written requests for single copies of the draft guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 2201, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your requests. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the draft guidance document.

Submit electronic comments on the draft guidance to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Laurie Muldowney, Center for Drug Evaluation and Research (HFD-003), Food and Drug Administration, Bldg. 51, Rm. 4154, 10903 New Hampshire

Ave., Silver Spring, MD 20993-0002, 301-796-1571.

SUPPLEMENTARY INFORMATION:**I. Background**

FDA is announcing the availability of a draft guidance for industry entitled "Limiting the Use of Certain Phthalates as Excipients in CDER-Regulated Products." This draft guidance provides the pharmaceutical industry with CDER's current thinking on the potential human health risks associated with exposure to DBP and DEHP. In particular, the draft guidance recommends that the pharmaceutical industry avoid the use of these two specific phthalates as excipients in CDER-regulated drug and biologic products, including prescription and nonprescription products. The recommendations in this guidance do not address the use of DBP or DEHP in other types of FDA-regulated products or exposure to DBP or DEHP due to the presence of any of these compounds as an impurity—including as a result of leaching from packaging materials.

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

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

Data from the National Health and Nutrition Examination Survey (NHANES) indicate widespread exposure of the general population to phthalates. Humans are exposed to phthalates by multiple routes, including inhalation, ingestion, and to a lesser degree absorption through the skin. Several observational human studies have reported an association between exposure to certain phthalates and adverse developmental and reproductive effects. The ubiquitous presence of phthalates in the

environment and the potential consequences of human exposure to phthalates have raised concerns, particularly in vulnerable populations such as pregnant women and infants.

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

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

There are alternatives to DBP and DEHP for use as excipients in CDER-regulated products. Manufacturers with products that contain DBP or DEHP should consider alternative excipients and determine if the alternative excipient they plan to use has been used in similar CDER-approved products and at what level.

The Inactive Ingredients Database provides information on excipients present in FDA-approved drug products, and this information can be helpful in developing drug products. As manufacturers reformulate their products, the listings for DBP and DEHP will be removed from the Inactive Ingredients Database.

This draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the Agency's current thinking on limiting the use of certain phthalates as excipients in CDER-regulated products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

II. Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) either electronic or written comments regarding this document. It is

only necessary to send one set of comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

III. The Paperwork Reduction Act of 1995

This draft guidance refers to previously approved collections of information found in FDA regulations. These collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520) and have been approved under OMB Control Numbers 0910–0014 and 0910–0001.

IV. Electronic Access

Persons with access to the Internet may obtain the document at either <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm> or <http://www.regulations.gov>.

Dated: February 28, 2012.

Leslie Kux,

Acting Assistant Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2011–D–0618]

Draft Guidances Relating to the Development of Biosimilar Products; Public Hearing; Request for Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of public hearing; request for comments.

SUMMARY: The Food and Drug Administration (FDA) is announcing a 1-day public hearing to obtain input on recently issued draft guidances relating to the development of biosimilar products (draft guidances). These draft guidances were issued by FDA as part of the implementation of the Biologics Price Competition and Innovation Act of 2009 (the BPCI Act). The BPCI Act establishes an abbreviated licensure pathway for biological products that are demonstrated to be biosimilar to, or interchangeable with, a reference product. FDA will consider the information it obtains from the public hearing in the finalization of these guidances. In addition, FDA is soliciting

public input regarding topics for future policies regarding biosimilars.

DATES: The public hearing will be held on May 11, 2012, from 8:30 a.m. to 5 p.m. Individuals who wish to present at the public hearing must register by April 11, 2012. Section V of this document provides attendance and registration information. Electronic or written comments will be accepted after the public hearing until May 1, 2012.

ADDRESSES: The public hearing will be held at FDA's White Oak Campus, 10903 New Hampshire Ave., Bldg. 31, Rm. 1503, Silver Spring, MD 20993.

Submit electronic comments to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Identify comments with the corresponding docket number found in brackets in the heading of this document.

Transcripts of the public hearing will be available for review at the Division of Dockets Management and on the Internet at <http://www.regulations.gov> approximately 30 days after the public hearing (see section VIII of this document).

A live Web cast of this public hearing may be seen at <http://www.fda.gov/Drugs/NewsEvents/ucm265628.htm> on the day of the public hearing. A video record of the public hearing will be available at the same Web address for 1 year.

FOR FURTHER INFORMATION CONTACT:

Sandra J. Benton, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6340, Silver Spring, MD 20993, 301–796–1042, Fax: 301–847–3529, email: biosimilarspublicmtg@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

On March 23, 2010, President Obama signed into law the Patient Protection and Affordable Care Act (Affordable Care Act) (Pub. L. 111–148). The Affordable Care Act contains the BPCI Act that amends the Public Health Service Act (the PHS Act) and other statutes to create an abbreviated licensure pathway for biological products shown to be biosimilar to, or interchangeable with, a reference product (see sections 7001 through 7003 of the Affordable Care Act).

The implementation of an abbreviated licensure pathway for biological products can present challenges given the scientific and technical complexities that may be associated with the larger and often more complex structure of

biological products, as well as the processes by which such products are manufactured. Most biological products are produced in a living system such as a microorganism, or plant or animal cells, whereas small molecule drugs are typically manufactured through chemical synthesis.

Among other things, section 351(k) of the PHS Act (42 U.S.C. 262(k)), added by the BPCI Act, sets forth the requirements for an application for a proposed biosimilar biological product. Section 351(k) defines biosimilarity to mean “that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components” and that “there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.” A 351(k) biosimilar application must contain, among other things, information demonstrating that the biological product is biosimilar to a reference product based upon data derived from analytical studies, animal studies and a clinical study or studies, unless FDA determines that an element described here is unnecessary in a 351(k) application.

II. Previous Public Hearing on Biosimilar Pathway

As part of our commitment to public outreach, FDA held a 2-day public hearing on the “Approval Pathway for Biosimilar and Interchangeable Biological Products” on November 2 and 3, 2010 (75 FR 61497, October 5, 2010) (November 2010 public hearing). The purpose of that public hearing was to seek comments on a number of issues relating to the implementation of the BPCI Act. Over 40 speakers presented at the public hearing. In addition to the presentations, FDA has received more than 60 public comments to the docket, which closed on December 31, 2010. Information on this prior public hearing, including the **Federal Register** notice, meeting transcripts, and public comments can be found at <http://www.regulations.gov> (Docket No. FDA–2010–N–0477). FDA carefully considered the presentations and public comments as it was developing the recently issued draft guidances (see section III of this document).

III. Draft Guidances

FDA has issued the following three draft guidances as part of its initial implementation of the BPCI Act based on public input at the November 2010 public hearing regarding priorities for issuing guidances: