

COURTNEY M. PRICE
VICE PRESIDENT
CHEMSTAR

December 4, 2002



Dockets Management Branch
Division of Management Systems and Policy
Office of Human Resources and Management Services
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD 20852

Re: Docket No. 02D-0325: Medical Devices Made with Polyvinylchloride (PVC) Using the Plasticizer di-(2-Ethylhexyl)phthalate (DEHP); Draft Guidance for Industry and FDA

Dear Sir/Madam:

The Phthalate Esters Panel of the American Chemistry Council is pleased to submit these comments in response to the above-referenced draft guidance document released by FDA's Center for Devices and Radiological Health (CDRH) Office of Device Evaluation. The Panel includes the major U.S. producers and some processors of di-(2-ethylhexyl)phthalate (DEHP) and other phthalate esters.¹

These comments supplement points made in an earlier letter submitted by the Panel on October 22, 2002. As stated in that earlier letter, the Panel believes strongly that the draft guidance document is not necessary and should be withdrawn. If it is not withdrawn, the Panel believes the draft guidance document should be substantially rewritten. Specific suggestions for how the draft guidance document might be revised, if it is not withdrawn, are included in these comments.

A. The draft guidance document pertaining to medical devices made with PVC containing DEHP is not needed and should be withdrawn

The Panel does not believe a guidance document pertaining to medical devices made with PVC containing DEHP is necessary. Rather, the Panel believes CDRH's Safety Assessment released in September 2001,² and the related Public Health Notification dated July

02D-0325

C13

¹ Members of the Panel include: BASF Corporation, Eastman Chemical Company, ExxonMobil Chemical Company, Ferro Corporation, PolyOne Corporation, Sunoco Inc. (R&M), and Teknor Apex Company.

² CDRH (2001). *Safety Assessment of Di(2-ethylhexyl)phthalate (DEHP) Released from PVC Medical Devices*. U.S. Food and Drug Administration, Center for Devices and Radiological Health, Rockville, MD [hereafter "Safety Assessment"].



12, 2002,³ which also contains recommendations, amply inform medical device manufacturers of the scientific issues pertaining to use of PVC containing DEHP in medical devices. Moreover, as explained further below, the draft guidance document is overly broad, is not consistent with CDRH's Safety Assessment, and is creating significant confusion in the marketplace. Furthermore, as discussed below and in Attachment A, new scientific information indicates that the Safety Assessment was very conservative and therefore that concerns for risks from DEHP exposure are less than indicated by that assessment. Under the circumstances, the Panel believes the appropriate action is for CDRH to simply withdraw the proposed guidance. The Panel does not believe there is a need to reissue the draft guidance in revised form.

B. If CDRH decides to issue revised draft guidance, then the draft guidance should be substantially revised

If CDRH continues to feel that a guidance document is necessary, then the Panel believes the draft guidance should be substantially revised. Specific suggestions are presented below. Further, the Panel believes CDRH should allow additional opportunity for public comment on any revised guidance document.⁴

1. CDRH should remove overly broad statements in the Draft Guidance that are creating confusion in the marketplace. As described in the Panel's previous letter, the Draft Guidance is causing confusion because of inconsistent statements within the document and inconsistencies between the document and the underlying safety assessment. The Draft Guidance acknowledges up front that "DEHP is recognized as an important chemical ingredient that affords PVC many of the physical properties that make the material optimally suited for use in many of today's medical devices." The Draft Guidance also acknowledges that while adverse effects have been observed in animal studies, "there are no human studies that show such effects." Further, the Draft Guidance states, "FDA recognizes that many devices with PVC containing DEHP are not used in ways that result in significant human exposure to the chemical." Elsewhere, however, the Draft Guidance contains very broad statements and recommendations that, read literally, appear to suggest that all medical devices made with PVC containing DEHP are a concern and should either be replaced or labeled. Based on discussions at a meeting with CDRH on October 10 to clarify the intent of the draft guidance, the Panel now understands that CDRH did not intend the Draft Guidance to have the broad reach that one might infer from a literal reading of the draft document. If CDRH issues revised guidance, it should eliminate all the overly broad statements that are causing confusion in the marketplace and that are not supported by its Safety Assessment.

2. The Draft Guidance should not apply to devices that are not expected to involve exposures at or above FDA's calculated Tolerable Intake levels. The

³ D. Feigal (2002). *FDA Public Health Notification: PVC Devices Containing the Plasticizer DEHP*. U.S. Food and Drug Administration, Center for Devices and Radiological Health, Rockville, MD.

⁴ See 21 CFR 10.115(g)(1)(v) (procedures for developing and issuing guidance documents).

draft guidance is excessively broad in that it purports to apply to medical devices that are not expected to involve exposures to DEHP above Tolerable Intake (TI) levels. The broad reach of the Draft Guidance clearly is not consistent with CDRH's underlying Safety Assessment, which does not demonstrate a likely safety concern for most uses of medical devices made with PVC containing DEHP. To the contrary, the concerns identified in the Safety Assessment pertain to *potential hazards* from use of specific medical devices in specific medical procedures (e.g., ECMO procedures applied to male neonates).

Indeed, CDRH's Safety Assessment does not support concern for large numbers of devices that fit within the categories listed in the draft guidance. The following are examples of applications for which estimated doses are below the relevant TI (*see* Safety Assessment Table 4-1, p. 47):

Examples of Devices with Estimated Exposures Below TI

IV tubing and catheters/cannulae for IV administration

- Infusion of crystalloid IV solutions (adult and neonate)
- IV infusion of drugs requiring pharmaceutical vehicles for solubilization (adult and neonate)
- Replacement blood transfusion
 - Neonate in NICU
 - Correction of anemia – chemotherapy and sickle cell patients (adult)
 - Surgical patient undergoing CABG (adult)
- Treatment of clotting disorders with cryoprecipitate (adult)

IV tubing and catheters/cannulae for dialysis

- Hemodialysis
- Peritoneal dialysis

IV tubing and catheters/cannulae for ECMO

- Heparinized ECMO circuits

IV tubing and catheters/cannulae for cardio-pulmonary bypass

- Orthotopic heart transplant (adult)

Bags for total parenteral nutrition

- TPN without added lipid (adult and infant)
- TPN with added lipid (adult)
- EVA bag with PVC tubing

Even where a procedure may result in an exposure above a TI, that does not necessarily indicate a significant health risk, since the TI is intended to be safe for repeated exposures over a long period of time, whereas many medical procedures occur infrequently or on a one-time basis. (See Attachment A.) Thus, for example, even in the case of exchange transfusion for a neonate, the CDRH Safety Assessment acknowledged that this treatment is rarely performed (p. 14), and that “the TI/dose ratio for this procedure [blood transfusion] is likely to overestimate the actual risk to these patients, since the TI is intended to be protective for long-term exposure, compared to relatively short-term exposure in acute transfusions.” (Safety Assessment, p. 5)

Moreover, since the Safety Assessment was released, new scientific information provides further evidence that higher TI levels for both parenteral and enteral exposure likely would be fully protective of patient health. The endpoint that is the basis for both parental and enteral TI's is reproductive tract effects in male rats. Studies in juvenile and adult primates had indicated that primates are much less sensitive to such effects than are rats, but there was concern that those studies might not have reflected potentially greater susceptibility in infants. A study of marmosets was recently completed in Japan, in which the animals were dosed from weaning to sexual maturation with 100, 500 or 2500 mg/kg/day of DEHP. Preliminary results communicated to the Panel are that there were no effects of DEHP on any target organ, there was no substantial accumulation of DEHP or its metabolites in the testis, and there was no gross or microscopic evidence of testicular changes. The study scientists therefore conclude that DEHP, at doses up to 2500 mg/kg/day, does not affect the maturation of the primate testis. More complete information about this study will be provided as it becomes available. The results of this study indicate that the TI values based on effects in rats are very conservative and that higher TI values would be protective of human health. In addition, the TI for enteral exposure is based on a study by Poon *et al.* (1997), but new research casts further doubt on the reliability of the findings reported in this study and indicates a higher enteral TI would be appropriate. This new information is discussed further in Attachment A to this letter.

More generally, CDRH's Safety Assessment incorporates a number of conservative (health protective) assumptions, such that CDRH should not assume that any exposure above a TI is indicative of a significant health risk. To the contrary, the weight of the scientific evidence supports the conclusion that human health risks from use of medical devices containing DEHP are likely far below the risk estimates derived from rodent studies. The Safety Assessment clearly does not demonstrate a need for a guidance document for medical devices that do not lead to exposures above TI levels. Even as to those devices that, based on very conservative methodology, might be expected to lead to exceedances of TI levels for some procedures, the likelihood of a significant risk to patients is very low. (See Attachment A.) A guidance document that urges device manufacturers to substitute materials about which less is known, and which may not perform as reliably as current products, is not necessarily in the best interests of patients.

3. Any revised guidance document should direct attention to the *medical procedures* that CDRH believes pose a potential concern. A list of devices, without a

clear connection to specific medical procedures, is misleading, because many medical devices are used in a wide variety of procedures, including both procedures that CDRH has identified as potentially of concern, and procedures that are expected to produce very low exposures relative to the tolerable intake levels calculated by CDRH. Thus, the Panel believes any guidance should focus on use of specific devices when used in specific medical procedures. Even with respect to specific procedures, however, CDRH should recognize that exceedances of the relevant TI from a single occurrence do not necessarily imply a health risk. (*See* discussion in Section B.2. and Attachment A of this letter.)

4. Consideration of reducing DEHP use should not be a design requirement. The Draft Guidance states: “Manufacturers should consider “minimizing patient exposure to DEHP” as a design requirement in their design control procedures (Quality System regulation, 21 CFR 820.30).” The Panel believes such a requirement is highly inappropriate. First, the requirement is overly broad – it asks manufacturers to address DEHP in all medical devices even though CDRH’s Safety Assessment indicates that only a handful of those devices, when used in certain procedures, pose potential concerns. Second, the requirement would make reduction of DEHP essentially a regulatory requirement, even though CDRH has not found its Safety Assessment to support regulatory action. Third, if reduction of DEHP is a design requirement, manufacturers may feel a necessity to reformulate away from DEHP to alternatives that are less well-tested, provide inferior performance, and/or are more costly, even though DEHP in the original formulation posed negligible health risks.

5. CDRH should not require labeling. The draft guidance document concedes that there is no legal basis for requiring labeling. The Panel does not believe CDRH should seek voluntary labeling when the underlying science does not support a labeling requirement, and a voluntary effort is likely to cause concern where no concern should exist.

If DEHP is singled out for labeling, that action could be taken as a signal that there is cause for concern about use of products containing DEHP, and may lead to inappropriate care decisions. Furthermore, a requirement to label DEHP may mislead health care providers or patients to conclude that components with no labeling are known to be “safe,” or at least safer than DEHP, when this may well not be the case. In most cases, it will signal only that other components that have not been as extensively studied as DEHP have been incorporated into the product. Disclosure of the presence of DEHP may thus be counterproductive and should not be required or recommended as a voluntary action.

6. Any guidance document should include greater recognition of the conservative nature of the TI levels in the underlying safety assessment. As already stated, the TI is intended to represent a safe exposure level assuming repeated daily exposures for an extended period, which is not realistic for most medical procedures. The TI also is based on animal studies, in the absence of human data demonstrating adverse effects, and assumes that humans may be more sensitive than laboratory animals, even though primate data provide strong evidence that the opposite probably is the case. For these reasons, even if use of a medical device in a particular procedure might result in exposures above the TI on the days that the procedure is performed, that does not mean there is a significant health risk to the patient.

The Panel believes the guidance document should expressly recognize the conservative (health protective) nature of the TI levels, and that true health risks may be much lower than indicated or even non-existent.

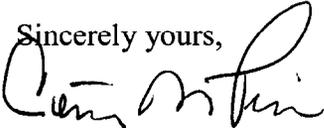
7. Any guidance document should state clearly that if medical device manufacturers consider alternatives to PVC made with DEHP, they should give adequate consideration to all performance, exposure or safety issues associated with any alternative materials that might be considered. As reflected in the DEHP Safety Assessment, DEHP has undergone extensive testing and there is an enormous amount of scientific information available to support that Safety Assessment. Medical device manufacturers should be cautioned about moving to alternative products that might lead to decreases in performance and in exposures to substances about which considerably less is known.

As explained in previous correspondence, alternative polymers and PVC made with alternative plasticizers are available, but these materials do not share all the performance advantages of PVC, and also typically cost more (certainly a relevant concern in this era of rising health care costs). Further, in the case of alternative plasticizers that might be used in PVC, these materials generally present similar opportunities for human exposure (or perhaps in some cases greater potential for exposure, because of greater solubility compared to DEHP), and much less toxicology data typically is available to support a safety assessment of those exposures.

C. Conclusion

The Panel appreciates CDRH's consideration of these comments. The Panel respectfully urges CDRH to withdraw the draft guidance document. The Panel does not believe a guidance document is needed; rather, the Panel believes FDA's Safety Assessment of DEHP in medical devices and its Public Health Notification dated July 12, 2002, amply address any concerns. However, if CDRH decides to reissue the draft guidance, then for reasons presented in these comments, the Panel believes the guidance should be substantially revised and submitted to additional public comment.

Any questions concerning these comments should be directed to Marian K. Stanley, Manager of the Phthalate Esters Panel, at 703-741-5623 or Marian_St Stanley@americanchemistry.com.

Sincerely yours,

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cc: Daniel G. Schultz, M.D.
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Dockets Management Branch
December 4, 2002
Page 7

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