Medical Devices Made With Polyvinylchloride (PVC) Using the Plasticizer di-(2-Ethylhexyl)phthalate (DEHP); Draft Guidance for Industry and FDA

Draft Guidance – Not for Implementation

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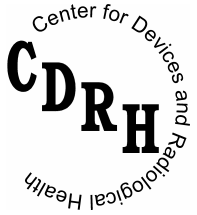

U.S. Department Of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Office of Device Evaluation

Preface

Public Comment

Comments and suggestions regarding this draft document should be submitted by December 5, 2002 to Docket No. 02D-0325, 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.

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Who should read this guidance document?

Manufacturers who fabricate their devices with polyvinlylchloride (PVC) using the plasticizer di-(2-ethylhexyl)phthalate (DEHP) should read this guidance.

What is the concern that this document is attempting to address?

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. DEHP is a chemical whose long-term effects on the human body are unknown. Through this guidance, FDA is offering suggestions on ways that you may reduce or eliminate risks that may be associated with DEHP. We are suggesting that you label certain devices with their DEHP content and consider eliminating the use of DEHP in certain devices that can result in high aggregate exposures in sensitive patient populations.

Does DEHP have adverse effects in humans?

Although the toxic and carcinogenic effects of DEHP have been demonstrated in laboratory animals, there are no human studies that show such effects. What we do know is that there are certain invasive medical procedures during which exposure to DEHP could exceed the levels that are not expected to cause any adverse health effects in patients.

Does FDA have concern with all devices that contain PVC?

No. As stated above, not all devices made with PVC contain DEHP. Further, FDA recognizes that many devices with PVC containing DEHP are not used in ways that result in significant human exposure to the chemical. Therefore, FDA is focusing attention on the small subset of medical devices where PVC containing DEHP may come in contact with the tissue of a sensitive patient population in a manner and for a period of time that may raise concerns about the aggregate exposure to DEHP. We believe that many devices used in Neonatal Intensive Care Units (NICUs) meet this criteria and should be a primary focus.

What types of CDRH-regulated devices typically may be of concern?

Again, the risks from DEHP-containing devices relate to: (1) the aggregate exposure and (2) the sensitivity of the exposed patient population. While devices used in neonates deserve particular attention, there may be other patient subgroups where DEHP exposure may be an issue. The following types of medical devices may contain PVC components, e.g., tubing or fluid containers, that could contain the chemical DEHP and expose sensitive patient populations:

Intravascular (IV) tubing and catheters/cannulae used in:

- ➔ IV administration
- ➔ dialysis
- ➔ extracoporeal membrane oxygenation (ECMO)
- ➔ cardio-pulmonary bypass (CPB) procedures.

Bags used to store and transport:

- ➔ enteral nutrition formulae
- ➔ total parenteral nutrition formulae.

Tubing used in enteral nutrition:

- ➔ nasogastric tubes
- ➔ gastrostomy tubes
- ➔ nasojejunal tubes

What does FDA recommend that you do if your device is made with PVC containing DEHP?

We encourage you to consider all mechanisms to reduce patient exposure to DEHP, particularly from those types of devices cited above. Specifically, we recommend that you consider the feasibility of replacing PVC containing DEHP with either alternative materials or plasticizers, or using coatings that may minimize patient exposure to DEHP. Manufacturers should consider "minimizing patient exposure to DEHP" as a design requirement in their design control procedures (Quality System regulation, 21 CFR 820.30). This step should contribute to an overall reduction in patient exposure to DEHP.

Do I need to submit a new 510(k) if I replace or modify the PVC in my device?

Generally, 510(k) holders do not need to submit 510(k)s to make materials changes of the nature discussed in this document. Nevertheless, you should refer to 21 CFR 807.81(a)(3) and our guidance document entitled, "*Deciding When to Submit a 510(k) for a Change to an Existing Device*" (http://www.fda.gov/cdrh/ode/510kmod.html), to determine whether any particular change requires the submission of a 510(k). It is your responsibility to determine whether you need to submit a 510(k) before making any particular change and to document your decision-making process in your design validation records.

What should I do if my device is exempt from 510(k) and I replace or modify the PVC in my device?

If your class I or class II device is exempt from the 510(k) requirements of the Federal Food, Drug, and Cosmetic Act, you should refer to the limitations of exemptions from section 510(k) to determine whether any particular change exceeds the limitations of the exemption, thereby requiring the submission of a 510(k). Generally, it is unlikely that materials changes of the nature discussed in this document would exceed the limitations of exemptions. The limitations of exemptions are codified at 21 CFR XXX.9, where XXX is the part of title 21 of the Code of Federal Regulations containing the particular device's classification, (e.g., 21 CFR 880.9 for Intravascular Administration Sets 21 CFR 880.5440).

Do I need to submit a PMA Supplement if I replace or modify the PVC in my class III device?

Generally, manufacturers of class III devices must assess each individual change to determine whether the change affects the safety and effectiveness of the device (21 CFR 814.39), thereby requiring the submission of a PMA supplement. However, FDA believes most manufacturers will not need to submit PMA supplements to make materials changes of the nature

discussed in this document. Manufacturers may conclude that such changes do not require prior FDA approval when the change is to a material known to be suitable for the particular use, and when verification and validation studies confirm that the device use requirements continue to be met. In cases where PMA supplements are not required, manufacturers should provide notification of the particular change in the next annual report to the PMA.

What if I choose not to change the material in my device? Should I revise the labeling to state the device contains DEHP?

Yes, we recommend that you clearly indicate through user labeling that your device contains DEHP. Although, at this time, FDA believes there is insufficient information to justify requiring device manufacturers to disclose the presence of this chemical in the device's labeling, there is considerable interest among some consumers and practitioners in mitigating any risks that exposure to DEHP may present. Disclosure can assist healthcare professionals in making informed decisions regarding an individual patient's exposure to DEHP.

Do I need to submit a new 510(k) or PMA Supplement if I revise the labeling to state the device contains DEHP?

This change does not require a new 510(k) or PMA Supplement. However, you should document the change in your device master record. For PMA devices, you should submit the change in your next Annual Report to the PMA.

Where can I find more information about medical devices and DEHP?

The Center for Devices and Radiological Health (CDRH) recently released a safety assessment, which can be found at http://www.fda.gov/cdrh/ost/dehp-pvc.pdf. In this document, the doses of DEHP received by patients undergoing various medical procedures are compared to the Tolerable Intake (TI) values for DEHP using ISO/DIS 10993-17 *Method for the Establishment of Allowable Limits for Leachable Substances*.