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TO: BERNARD A SCHWETZ HF-1

FROM: VARIOUS ORGANIZATIOIS

SYNOPSIS: VARIOUS GROUPS UNDER HEALTHCARE WITHOUT HARM'S ADDRESS WRITE TO
SUPPORT 99P-2077 - REGARDING LABELING OF DEHP CONTAINING PVC
DEVICES

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| ASSIGNED TO | ACTION | DUE DATE |
|--------------------|---------------------------|-----------------|
| ----- HFA-305 | ----- NECESSARY ACTION | ----- |
| HFZ-1 | FOR YOUR INFORMATION | |

March 7, 2002

Bernard Schwetz, DVM, PhD
Acting Commissioner
Food and Drug Administration
5600 Fishers Lane, Room 14-71
Rockville MD 20857

Dear Dr. Schwetz:

The undersigned individuals and organizations are writing to encourage the FDA to take prompt action on your agency's recently released Safety Assessment of Di (2-ethylhexyl) phthalate (DEHP) Released from PVC Medical Devices. For the reasons stated below and as requested in the petition to FDA from Health Care Without Harm, we urge the FDA to label all DEHP-containing PVC medical devices that could result in exposures to patients above the FDA's tolerable intake values, or result in non-systemic effects of concern. We also urge you to provide additional risk management and communication tools to clinicians to assist us in providing safe care to our patients.

Although the agency's September 5, 2001 Safety Assessment does not attempt to quantitatively assess the risk posed by exposure of patients to DEHP, it concludes that some uses of medical products made from polyvinyl chloride (PVC) will expose patients to potentially unsafe amounts of the plasticizer (DEHP). The FDA concluded that exposures to patients during the following medical procedures may exceed the tolerable intake of DEHP: Adults and infants undergoing extracorporeal membrane oxygenation (ECMO) therapy; infants undergoing exchange transfusions; all patients receiving enteral nutrition; infants receiving total parenteral nutrition (TPN); adults undergoing cardiopulmonary bypass procedures; and nursing infants of mothers on hemodialysis.

Further, the Safety Assessment notes that aggregate exposures to DEHP from multiple devices can also result in doses that exceed the tolerable intake. For example, the FDA calculates that infants receiving multiple treatments in neonatal intensive care units may be receiving 20 times more DEHP from medical device related sources than the calculated tolerable intake. The Agency's documents states, " it is important to assess the potential risk of patients in various clinical scenarios by taking into account aggregate exposure to DEHP from multiple devices." The FDA safety assessment notes that DEHP leaching from respirators, endotracheal tubes, urinary catheters, oxygen masks, and gloves add to the total exposure.

The report also notes that non-systemic adverse effects of DEHP in patients can be clinically significant, although none of these was considered in the derivation of the tolerable intake values. For example, the safety assessment points out that DEHP can alter the hemocompatibility of PVC tubing, causing platelet aggregation and complement activation, resulting in clinically important microemboli. Brain infarcts and dysfunction have been attributed to DEHP leaching from PVC tubing, as well as infarcts of lungs and kidneys. DEHP can also result in adsorption of drugs to PVC tubing and may have a role in the development of peritoneal sclerosis in patients undergoing peritoneal dialysis. Questions have also been raised about the effects of DEHP exposure on the liver and lungs. Some

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studies suggest a link between DEHP leaching and cholestasis in infants supported by ECMO, hepatotoxicity observed in infants receiving TPN, and the risk of bronchopulmonary dysplasia in premature newborns. The FDA's risk communication strategy must include education on these questions.

It also remains important to recognize that, beyond the specifically identified groups, the entire population is exposed to background levels of DEHP of approximately 3-30 micrograms/kg/day, largely from dietary sources. This raises a concern for additional populations, in particular women of childbearing age. Women of reproductive age in the general population are routinely exposed to background levels of DEHP that constitute an estimated 25% (and perhaps as much as 75%) of the FDA's oral tolerable intake, prior to receiving any medical treatment.

Consequently, when considering all sources of exposure, pregnant women undergoing medical procedures will more readily be exposed to levels of DEHP that exceed the FDA's tolerable intake, putting their developing fetuses at risk. FDA must develop an action plan that does not focus only on the infant in a Neonatal Intensive Care Unit but also for women who are pregnant or who may be pregnant and the child in utero.

Although the FDA points out that simultaneous co-exposure to DEHP and its more toxic metabolite MEHP can occur in some patients it does not include exposure to MEHP in its TI/dose ratio calculations. DEHP is converted to MEHP in blood or crystalloid solutions before the product is administered to the patient. When crystalloid IV solutions are infused, for example, considering the increased potency of MEHP as a testicular toxicant, the FDA estimates that the TI/dose ratio would drop from 120 to 4. Given that pregnant women may already have background exposures to DEHP that can be as high as 75% of the TI, special consideration needs to be given to the potential additional effects of DEHP in crystalloid IV solutions for this population.

The FDA document notes several factors that increase DEHP leaching from PVC medical devices. The presence or co-infusion of lipids, heating, storing for longer time periods, storing at warmer temperature, and agitating are all listed as such factors. FDA must educate health care providers about clinical practices that lead to higher DEHP exposures and the availability of alternatives that allow warming, storing, agitating and the addition of lipids without releasing DEHP.

Given the above, we urge the FDA to initiate rulemaking or issue a guidance consistently requiring labeling of:

* All PVC medical devices that, according to the FDA Safety Assessment, may under some circumstances leach DEHP at levels approaching or in excess of tolerable intake including those used to administer total parenteral nutrition with added lipids to infants; to transfuse blood during trauma, ECMO or in exchange transfusion to neonates; during cardiopulmonary bypass or to provide enteral nutrition;

* All PVC medical devices that may pose, when used by pregnant or potentially pregnant women, prenatal exposures to DEHP at any level, given already significantly elevated background exposures;

- * All PVC medical devices that may be utilized in conjunction with breast pumps and breast milk and could leach DEHP into the breast milk;
- * All PVC medical devices that may contribute to levels of DEHP in the milk of breast feeding women where the Safety Assessment indicates that the levels of DEHP may approach or exceed the tolerable intake (TI) of the breast feeding infant;
- * All PVC medical devices that may leach DEHP when used intentionally or inadvertently with lipid-containing nutrition or lipophilic drugs;
- * All PVC medical devices that may leach DEHP and add to the DEHP exposure of patients WHO are also undergoing a medical procedure that already, according to the FDA Safety Assessment, may under some circumstances leach DEHP at levels approaching or in excess of tolerable intake;
- * All medical devices that may cause non-systemic effects as indicated in Annex D of the FDA Safety Assessment of DEHP medical devices.

In addition, we urge the FDA to:

- * Develop a market information and education program that informs health care providers of the potential hazards of DEHP and the availability of alternatives that either are DEHP-free, or are not capable of leaching DEHP.
- * Maintain an up-to-date inventory on the FDA website and in written agency publications, such as FDA Consumer, of the medical devices on the market that leach DEHP and any FDA-approved non-DEHP-containing substitute known to be available.

As the FDA considers these matters we believe that it is important for the agency to consult not only with device manufacturers but also with clinicians whose practices put these devices into use. Having become aware of the risks of DEHP exposures in some patients, we find it problematic to be unable to identify those medical products that may leach the compound. We remain available to the agency to discuss strategies for reducing these risks.

Thank you for your prompt attention, and your commitment to the health of the nation's patients.

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Docket # 99P-2077/CP1

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