SANFORD J. LEWIS, ATTORNEY

July 24, 2007

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Andrew C. Von Eschenbach, M.D.
Commissioner, Food and Drug Administration
Parklawn Building, Room 1471, 5600 Fishers Lane
Rockville, MD 20877

Dear Dr. Von Eschenbach,

Enclosed find four copies of a petition from Health Care Without Harm for rulemaking to require the labeling of medical devices containing DEHP, accompanied by a letter of support and endorsement from numerous organizations including the American Medical Association (AMA), American Nurses Association (ANA), American Public Health Association (APHA), Association of Women's Health, Obstetric and Neonatal Nurses (AWOHNN), Physicians for Social Responsibility (PSR), and American College of Nurse Midwives (ACNM).

Please contact me at 413 549-7333 if you have any questions. Thank you for your attention to this matter.

Sincerely,

Sanford Lewis

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ANDREW C. VON ESCHENBACH, M.D.
Commissioner, Food and Drug Administration
Parklawn Building, Room 1471
5600 Fishers Lane
Rockville, MD 20877

Dear Dr. Von Eschenbach:

In November, 2006, the National Toxicology Program issued a final report, making an authoritative statement confirming the potential for exposures to Di(2-ethylhexyl)phthalate (DEHP) in medical devices to undermine the normal development of the male reproductive tract. Yet, many medical device manufacturers are failing to disclose DEHP content on product labels. As a result, healthcare providers and institutions are severely handicapped in their efforts to prevent exposures to DEHP for vulnerable populations. **We are writing in support and endorsement of the enclosed petition, requesting that the Food and Drug Administration initiate a rulemaking or issue a guidance requiring medical device manufacturers to consistently label all medical device products containing polyvinyl chloride (PVC) that may expose patients to DEHP.**

The FDA's Public Health Notification issued in July, 2002, urged health care providers to reduce the use of DEHP-containing devices for certain patient groups. Since then, health care institutions nationwide have been struggling to follow FDA recommendations to adopt safer alternative products. Since the FDA has failed to finalize guidance to industry regarding DEHP, and failed to require labeling, many manufacturers are not labeling their DEHP-containing devices. The absence of DEHP labeling has made it difficult and time consuming for practitioners and supply staff to follow the FDA recommendations. In failing to mandate DEHP labeling by manufacturers, or to require its phase out, this has, in effect, shifted the costs of the transition to the health care sector and extended the timeframe that patients, including the most vulnerable neonatal populations, receive DEHP exposures during critical health care treatments. In some cases, it may make it impossible to fully comply with the FDA's own July 2002 Public Health Notification. For instance, many smaller scale health care operations and offices that lack the research and logistical staff of larger institutions are left unable to effectively implement the FDA's recommendations.

As the attached statements from hospitals indicate, DEHP labeling would help make it possible for hospitals to transition to safer alternatives and to maintain DEHP-free treatment for vulnerable populations in the face of a marketplace that is constantly changing and introducing new products. Healthcare providers and their institutions strive to provide the safest level of care for their patients. Labeling of DEHP-containing devices is a missing link needed to enable providers to implement your advisory, and provide the protection from potential harm to developing males and other vulnerable patients that the FDA has recommended.

Last spring, over 100 hospitals signed the Health Care Without Harm pledge committing to phase out the use of PVC/DEHP medical device products. In December, 2006, the American Medical Association passed a resolution, that in part, 'encourages hospitals and physicians to

reduce and phase out polyvinyl chloride (PVC) medical device products, especially those containing Di(2-ethylhexyl)phthalate (DEHP), and urges adoption of safe, cost-effective, alternative products where available (Res. 502, A-06).

This issue is crucial for the health of infants, children, and pregnant women -- the populations that NTP and FDA have identified as most vulnerable to DEHP exposures. We are joined in our concerns by the signatories below, representing health professionals across the country. Please act to mandate labeling for medical device products containing DEHP. Thank you for your time and attention to this matter.

Sincerely,

American Medical Association (AMA)
American Nurses Association (ANA)
American Public Health Association (APHA)
Association of Women's Health, Obstetric and Neonatal Nurses (AWOHNN)
Physicians for Social Responsibility (PSR)
American College of Nurse Midwives (ACNM)
Health Care Without Harm

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Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1-23,
12420 Parklawn Drive
Rockville, MD 20857

CITIZEN PETITION BEFORE THE UNITED STATES FOOD AND DRUG ADMINISTRATION

HEALTH CARE WITHOUT HARM
1901 N. Moore Street Suite 509
Arlington, VA 22209

Petitioner,
Before ANDREW C. VON ESCHENBACH, M.D.
in his official capacity as,
Commissioner
Food and Drug Administration
Parklawn Building
Room 1471
5600 Fishers Lane
Rockville, MD 20877

CITIZEN PETITION FOR A FOOD AND DRUG ADMINISTRATION REGULATION OR GUIDELINE TO LABEL MEDICAL DEVICES THAT LEACH DEHP PLASTICIZERS

Pursuant to the Administrative Procedure Act and Food, Drug and Cosmetic Act, 21 U.S.C. 360j(e), granting the FDA the power to restrict the use of medical devices and to require labeling, and 21 USC sec. 352, regulating the misbranding of Drugs and Devices, and the Food and Drug Administration's (FDA) implementing regulations on citizen petitions, 21 CFR 10.30 and 10.20, the undersigned submits this citizen petition for rulemaking and collateral relief under the Federal Food Drug and Cosmetic Act to respectfully request the Commissioner to promptly undertake the following actions:

> Initiate a rulemaking or issue a guidance requiring medical device manufacturers to consistently label all medical devices that may cause patient exposure to DEHP and which may be used in settings that, according to the National Toxicology Program, present a concern that such exposures may interfere with the normal development of the male reproductive tract. This

includes any devices that may be used with pregnant women or in treatment of infants, regardless of whether they are also used with other patient groups.

The guidance or regulation should require prominent, clearly worded labeling as to the potential for exposure to DEHP. Medical devices that leach DEHP shall include in a box a prominent, clearly-worded warning label on the device stating:

i. A statement that the device contains and may leach DEHP;
ii. A statement that exposures, including prenatal and postnatal exposures, may interfere with the normal development of the male reproductive tract; and
iii. Identification of the populations for whom alternative devices may be appropriate including pregnant or breast feeding women, male infants and boys through puberty.

The Petitioner submitted a similar petition in June, 1999 and a petition for reconsideration in October 2001. The initial petition and petition for reconsideration were rejected by the FDA based on the rationale that the agency was preparing a draft guidance and risk communication strategy for devices containing DEHP that it believed would adequately address the concerns. In 2002 the FDA issued a public health notification directed to health care providers and a draft guidance directed to manufacturers of medical devices. The FDA never issued a final guidance, and never required medical device manufacturers to label products containing and leaching DEHP.

Concurrently and subsequently, the National Toxicology Program has further studied this issue and confirmed the risks associated with human exposure to medical devices containing DEHP. The latest findings of the NTP necessitate action under the Federal Food Drug and Cosmetic Act. In addition, several years of experience by health care providers in attempting to act consistent with the recommendations of the agency's public health notification further demonstrate the need for a product labeling mandate.

I. Petitioner

Petitioner Health Care Without Harm, (HCWH), a coalition of health, religious, labor, and environmental organizations, hereby files this petition on behalf of its 462 member organizations. HCWH is a broad-based international coalition seeking to reform the health care industry by promoting comprehensive pollution prevention practices, supporting the development and use of environmentally safe materials, technology and products, and educating and informing health care institutions, providers, workers, consumers and all affected constituencies about the environmental and public health impacts of the health care industry and solutions to these problems. HCWH is located at 1901 N. Moore Street, Suite 509, Arlington, VA 22209. A list of member organizations is attached to this petition as Exhibit 1.

II. Analysis of Technical Issues

A. Medical Devices in use in the U.S. contain DEHP plasticizers that leach from the products during use.

Polyvinyl chloride (PVC or vinyl) is used in a range of medical devices, such as intravenous (IV) and

blood bags and other storage containers, and medical tubing and catheters. Di-ethylhexyl phthalate (DEHP) is a plasticizer widely used to make PVC medical products soft and flexible. PVC medical devices may contain up to 80% DEHP by weight.

Because DEHP is not chemically bound to the polymer, the plasticizer can leach out during normal use. This extraction occurs either by the DEHP directly leaching out of the PVC product or when an extracting material (blood, IV fluids) diffuses into the PVC matrix, dissolves the plasticizer, and the two diffuse out together. The most important factors in DEHP leaching from medical devices are temperature, concentration of phthalate, agitation, storage time, and surrounding media. More than 10% of the DEHP contained in a PVC medical device may leach during medical treatment. DEHP is leached from PVC blood bags, IV bags and tubing into blood, blood products, and medical solutions, often in significant concentrations.

B. The National Toxicology Program concluded that exposures to DEHP in current medical procedures presents serious and significant concerns regarding development of the male reproductive tract.

1. The NTP is one of the nation's most credible source on toxicology concerns.

The National Toxicology Program represents one of the most credible and prestigious analytical bodies in the federal government, existing to provide authoritative assessment of toxicology issues. The program was created as a cooperative effort to coordinate toxicology testing programs within the federal government, strengthen the science base in toxicology, develop and validate improved testing methods and provide information about potentially toxic chemicals to health, regulatory, and research agencies, scientific and medical communities, and the public.

According to the NTP website, the need for the NTP arose out of increasing scientific, regulatory, and Congressional concerns about the human health effects of chemical agents in our environment. Many human diseases were thought to be directly or indirectly related to chemical exposures; therefore, it was thought that decreasing or eliminating human exposures to those chemicals would help prevent some human disease and disability.

2. The NTP assessment is an authoritative statement of the severity of concerns regarding exposures to DEHP in medical devices.

In 2006, the National Toxicology Program completed a several year-long assessment and published a monograph on the potential human reproductive and developmental effects of DEHP. In brief, the assessment (Exhibit 2) concluded that:

- "There is serious concern that certain intensive medical treatments of male infants may result in DEHP exposures levels that affect development of the male reproductive tract."
- "There is concern for adverse effects on development of the reproductive tract in male offspring of pregnant and breastfeeding women undergoing certain medical procedures that may result in exposure to high levels of DEHP."
- "There is concern for effects of DEHP exposure on development of the male reproductive tract

for infants less than one year old."

- "There is some concern for effects of DEHP exposure on development of the reproductive tract of male children older than one year."

- "There is some concern for adverse effects of DEHP exposure on development of the male reproductive tract in male offspring of pregnant women not medically exposed to DEHP."

- "There is minimal concern for reproductive toxicity in adults exposed to DEHP at 1-30 ug/kg/day. This level of concern is not altered for adults medically exposed to DEHP."

The NTP assessment reaffirms and amplifies prior conclusions of the Food and Drug Administration from its own 2001 safety assessment, that it is appropriate to reduce exposures to DEHP-containing devices during medical procedures for male infants and children, for pregnant women who may have male offspring, and for women who are breast feeding male infants. The NTP monograph removes any question regarding the need for FDA action to eliminate exposure of the most vulnerable populations to DEHP. Clearly, the NTP brief is intended as a neutral source to be used by decision makers. As it states:

> The NTP brief on DEHP presents the NTP's opinion on the potential for exposure to DEHP to cause adverse reproductive or developmental effects in people. The NTP brief is intended to provide clear, balanced, scientifically sound information. It is based on information about DEHP provided in the expert panel report, public comments, comments from peer reviewers and additional scientific information available since the expert panel meeting.

The expert panel report conducted by the Center for the Evaluation of Risks to Human Reproduction within the National Toxicology Program was the technical foundation for the NTP brief on DEHP. While there have been industry-funded studies that have been touted by medical device manufacturers to minimize concern about DEHP-containing devices, the NTP study presents the most authoritative and independent assessment yet regarding the impacts that DEHP is likely to have on human health.

The NTP report and its expert panel's analysis are submitted as Exhibit 2 to this petition, providing the needed documentation of the risks of exposure to DEHP consistent with FDA Rule 21 CFR 10.20 (c).

In addition we note that the Food and Drug Administration' own Safety Assessment of DEHP identified a number of uses and populations where the exposure is expected to exceed a no adverse effects level.

C. Hospitals and health care providers believe the medical device industry labeling of devices containing DEHP is necessary to implement effective health care approaches regarding DEHP-containing medical devices.

As documented in the enclosed statements (Exhibit 3), the health care providers and hospitals that have an obligation to implement the FDA's DEHP Public Health Notification believe that it is necessary and appropriate to require manufacturers to label medical devices containing DEHP.

Through its public health notification, the Food and Drug Administration has encouraged health care

providers to reduce the use of DEHP-containing medical devices for vulnerable populations. Several major health care institutions report in these letters that they have successfully eliminated DEHP-containing medical devices in their neonatal intensive care units. However, the FDA has not required medical device manufacturers to institute labeling for DEHP-containing devices. In the absence of an FDA requirement, many manufacturers are not voluntarily labeling their medical devices that contain and leach DEHP. As these letters demonstrate, this means that health care providers must consume expensive staff time in conducting research, facility by facility and unit by unit, to implement the FDA's recommendations at the point of delivery of services. The FDA public health notification is ineffectual unless accompanied by requirements for labeling.

The letter from Kaiser Permanente notes:

> The National Toxicology Program's findings on di-ethyl hexyl phthalate (DEHP) are one example where KP has concluded there is sufficient evidence that DEHP is a potential reproductive toxicant to neonatal males. Accordingly, KP undertook thorough investigations of products already in use in KP Neonatal Intensive Care Units (NICUs) and subsequently completed field evaluations of identified non-DEHP products. Today, non-DEHP alternatives have replaced DEHP products in all neonatal applications for which they are available in KP's 34 NICU units.
>
> We are proud of our phase-out of DEHP devices, but it must be said that the process would have proceeded much more quickly if labeling of DEHP devices was required by FDA.

The letter from Miller's Children's Hospital (Long Beach, CA) notes:

> Our own experience sheds light on the difficulties hospitals face when trying to protect patients from DEHP exposure. Our Central Supply Manager reports that her queries to medical device manufacturers customer service representatives about DEHP content in their products yields the response that the customer service reps don't even know what she is talking about. They don't know what DEHP is, which requires a referral to technical support and leads to precious lost time.
>
> We cannot be advocates for patient safety when vital information is unavailable. To not have information about DEHP content in devices that are commonly used in patient care is an injustice to both patients and healthcare providers.

The letter from Children's Hospital and Regional Medical Center (Seattle, WA) notes:

> Even with a few dedicated staff, a receptive purchasing department (the cost of DEHP-free supplies can be more than those not containing this chemical) and vendors, we are still working hard to remove all such equipment and devices from our hospital. Our efforts to do this work would have been greatly facilitated had the medical device companies been more open and transparent with their labeling of DEHP-containing products, or better yet, taken the initiative to make DEHP-free products available.

As Mary Frances D. Pate, DSN, RN wrote about her tenure as the Pediatric Intensive Care Unit (PICU), Clinical Nurse Specialist, at Doernbecher Children's Hospital, a part of the Oregon Health &

Sciences University, (a full-service children's hospital in the Pacific Northwest that offers a comprehensive program of specialties with full-spectrum pediatric care for hospitalized children):

> Becoming educated on the subject was relatively easy, however identifying available alternatives, even though they existed, was not. One of the biggest challenges we faced was deciphering which of the products contained DEHP and which did not. Many of these products are not labeled and PICU/NICU staff spent countless hours on the phone with medical device manufacturers trying to obtain the information.

The only way to consistently allow providers to avoid DEHP-containing devices is to ensure that the devices themselves are labeled. In addition, the current voluntary labeling approach dramatically increases the costs to the health care sector of researching and managing these issues.

Even though many hospitals have eliminated DEHP-containing devices in one relevant area, neonatal intensive care units, this does not eliminate the array of harmful exposures of concern. Because pregnant women or young boys may be treated ANYWHERE in health care institutions, a much broader ability to easily identify DEHP-containing devices is needed. While identification of the devices within narrow parts of health care institutions has proven feasible with extensive effort, extending the device exclusion to the array of exposures situations of concern that arise throughout health care institutions necessitates labeling.

Even exclusions of DEHP devices in neonatal uses is rendered difficult and in some cases unlikely to occur without medical device labeling. While a number of large facilities have implemented exclusion of devices from neonatal units, smaller health care operations, including doctors' offices and clinics, may be unable to implement the FDA public health notification since they lack the substantial resources applied by larger institutions to ensure implementation. In addition, maintenance of DEHP exclusions in facilities of all scales is also a problem. Where health care facilities use both DEHP and non-DEHP devices, in the absence of labeling the consistent exclusion of the DEHP-containing devices in sensitive populations presents substantial logistical burdens.

D. Lack of labeling allows confusion and misleading statements when companies defend safety of their DEHP-containing devices.

Further, the medical device manufacturers continue to engage in communications that confuse health care providers, by asserting the lack of proof and adequacy of safety of DEHP-containing devices. For instance, see Baxter's website statement at http://www.baxter.com/about_baxter/news_room/positions_policies/sub/pvc_position_statement.html where Baxter states among other things that:

> Based on more than 40 years of safe and effective clinical use, and the large body of scientific data that supports its use, Baxter believes that PVC is the material of choice in many products. PVC has a long history of use in a variety of medical products, such as contact lenses, intravenous bags, oxygen tents and catheters. These products have undergone strict regulatory review by many government and independent health agencies throughout the world, including the U.S. Food and Drug Administration. The safety of these materials has been confirmed by more than 40 years of use, with five to seven billion patient days of acute exposure and one to two billion patient days of chronic exposure without any indication of adverse effects.

The FDA's failure to require labeling that makes an affirmative statement regarding the health concerns relative to DEHP devices makes the device manufacturers' defensive scientific statements such as Baxter's particularly problematic and confusing to providers. To avoid misleading health care providers, the FDA must require labeling of DEHP-containing devices.

III. Analysis of Current FDA Regulations and Guidance.

A. The FDA public health notification urged health care providers to seek alternatives to DEHP devices.

The FDA Public Health Notification listed a set of procedures posing the greatest risk of potentially harmful exposures for vulnerable populations from DEHP. It stated that:

> The following procedures have been identified as posing the highest risk of exposure to DEHP:
>
> 1. exchange transfusion in neonates
> 2. ECMO in neonates
> 3. total Parenteral Nutrition (TPN) in neonates (with lipids in PVC bag)
> 4. multiple procedures in sick neonates (high cumulative exposure)
> 5. hemodialysis in peripubertal males
> 6. hemodialysis in pregnant or lactating women
> 7. enteral nutrition in neonates and adults
> 8. heart transplantation or coronary artery bypass graft surgery (aggregate dose)
> 9. massive infusion of blood into trauma patient transfusion in adults undergoing ECMO

It then stated that:

> For some of the above procedures, PVC devices that do not contain DEHP can be substituted, or devices made of other materials (such as ethylene vinyl acetate (EVA), silicone, polyethylene or polyurethane) can be used, if available. If PVC devices containing DEHP must be used, you may be able to minimize exposure to DEHP by, for example, using the freshest possible blood products stored at the lowest possible temperature, or by using heparin-coated ECMO circuits.
>
> We recommend considering such alternatives when these high-risk procedures are to be performed on male neonates, pregnant women who are carrying male fetuses, and peripubertal males. One source for identifying alternative devices that do not contain DEHP-plasticized PVC is http://www.sustainablehospitals.org, associated with the University of Massachusetts Lowell.

This approach, while providing reference to a useful list of alternatives, does not enable hospitals to distinguish, at the point of delivery of health care services, whether an individual device may be exposing a higher risk patient to DEHP. The failure to require labeling of such devices means that health care providers are at disadvantage at the point of delivery of service.

In 2001 and 2002 the FDA wrote to Health Care Without Harm that it was denying a prior petition, and petition for reconsideration, which sought a regulation or guidance regarding labeling of DEHP-

containing devices. The agency asserted at that time that its method of dealing with this issue would be to implement a risk communication strategy. The primary elements of this strategy were the Safety Assessment, September 2001 and the Public health notification issued July 12, 2002 and directed to health care providers, and a **draft** guidance to manufacturers (labeled Draft Guidance – Not for Implementation) issued September 2002 . The draft guidance to manufacturers would **encourage** manufacturers to find alternatives to DEHP, and "**suggest**" but not require that manufacturers label medical devices containing DEHP:

> **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.
>
> FDA, Medical Devices Made With Polyvinylchloride (PVC) Using the Plasticizer di-(2-Ethylhexyl)phthalate (DEHP); Draft Guidance for Industry and FDA, September 2002.

In the subsequent four years the FDA never issued a **final** guidance to manufacturers "for implementation," and many manufacturers have continued to use DEHP in medical device and have not labeled their products as containing DEHP despite the "suggestion" in the draft guidance. Enough time has passed to conclude that the FDA's strategy to date has been a failure -- it has not resulted in labeling of devices sufficient to allow health care providers to implement the public health notification at the point of delivery of services; a mandatory labeling approach is necessitated in the absence of another proven strategy, in order for the FDA to fulfill its obligation to the public health and safety.

IV. National Environmental Policy Act Assessment and Certification

The National Environmental Policy Act, 42 USC §4331, imposes a continuing obligation on federal agencies to take account of the environmental impacts of their significant actions and decisions that may affect the human environment. Petitioners assert and certify that this petition is exempt from environmental assessment under 21 CFR 25.30(k), which exempts the establishment or repeal by regulation of labeling requirements for marketed articles if there will be no increase in the existing levels of use or change in the intended uses of the product or its substitutes. Although petitioners believe this petition is exempt as noted from environmental assessment requirements, in the event that the FDA does not agree with this conclusion, we provide the following environmental assessment. To our knowledge, there are no detrimental environmental impacts of this labeling requirement.

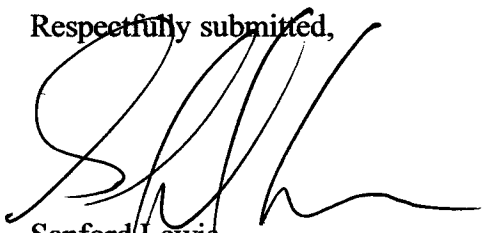
CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data known to the petitioner which are unfavorable to the petition.

As established in 21 C.F.R. § 10.30(e)(2), petitioners request that the agency provide an answer to this

citizen petition within 180 days.

Respectfully submitted,



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PO Box 231
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(413) 549-7333
Attorney for
Health Care Without Harm
Dated: March 15, 2007

Exhibits to Petition by Health Care Without Harm
for Labeling of Medical Devices Containing DEHP
July 23, 2007

1. Health Care Without Harm Member Organizations

2. National Toxicology Program-CERHR, Monograph on the Potential Human Reproductive and Developmental Effects of DEHP

3. Supporting Letters from Hospitals and Health Care Institutions

   Endorsers' transmittal letter
   Premier Inc.
   Miller Children's Hospital
   Novation
   Oregon Health & Science University
   Magee Women's Hospital of UPMC
   Abington Memorial Hospital
   Good Shepherd Medical Center
   Evergreen Healthcare
   Children's Hospital and Regional Medical Center, Seattle, WA
   Kaiser Permanente
   Catholic Healthcare West