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HEALTH CARE WITHOUT HARM
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PETITION FOR RECONSIDERATION REGARDING CITIZEN PETITION FOR A FOOD AND DRUG ADMINISTRATION REGULATION OR GUIDELINE TO LABEL MEDICAL DEVICES THAT LEACH PHTHALATE PLASTICIZERS AND TO ESTABLISH A PROGRAM TO PROMOTE ALTERNATIVES

UNITED STATES FOOD AND DRUG ADMINISTRATION
Docket Number 99P-2077/CP1

Pursuant to the Food and Drug Administration's (FDA) regulations, 21 CFR 10.33, the undersigned submits this petition for reconsideration of the decision of the Commissioner of Food and Drugs in Docket No. 99P-2077/CP1.

DECISION INVOLVED

Health Care Without Harm submitted a petition to the FDA on June 14, 1999 for a regulation or guideline to label medical devices that leach phthalate plasticizers and to establish a program to promote alternatives. On September 5, 2001, the FDA issued its response to the petition in a letter to Health Care Without Harm from Linda S. Kahan (FDA Reply). To summarize, the FDA Reply states that the agency based its decision on

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the HCWH petition on its Safety Assessment of DEHP, that the FDA will conduct risk communication measures based on the Safety Assessment, and that the agency is considering various potential regulatory and risk reduction responses based on the concerns raised in the Safety Assessment. The FDA Reply also states that the agency has denied the HCWH petition:

> Although we are denying your petition, we recognize that risk reduction strategies are appropriate for some medical procedures that employ PVC devices, and we are currently exploring options to reduce exposure of some patient populations to DEHP. These options, as mentioned above, may include new labeling for selected devices.

ACTION REQUESTED

Because the FDA's own evaluation of these issues indicates serious potential harms to health from DEHP-containing medical devices, resulting in a legal duty of the FDA to ensure adequate labeling and other precautions, we petition the FDA to reconsider its reply to the HCWH petition and to take the following actions:

1. Grant the petition in part;

2. As required by FDA regulations on citizen petitions, take formal action to implement responsive action, including identifying the agency's commitments including timelines, benchmarks, medical devices and areas of utilization targeted, etc.;

3. Initiate rulemaking or issue a guidance consistently requiring labeling of:

   a. 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;

b. All PVC medical devices that may pose, when used by pregnant or potentially pregnant women, prenatal exposures to DEHP at any level;

c. All PVC medical devices that may be utilized in conjunction with Breast Pumps and Breast Milk and leach DEHP into the breast milk;

d. 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;

e. All PVC medical devices that may leach DEHP when used intentionally or inadvertently with lipid-containing nutrition or lipophilic drugs;

f. All PVC medical devices that may leach DEHP that could add to the DEHP exposure of patients that are also undergoing a medical procedure that, according to the FDA Safety Assessment, may under some circumstances leach DEHP at levels approaching or in excess of tolerable intake; and

g. All medical devices that may cause nonsystemic effects as indicated in Annex D of the FDA Safety Assessment of DEHP medical devices.

In each of these contexts, include prominent, clearly worded labeling as to the potential for DEHP or other phthalates to leach, and the potential for health effects from exposure to DEHP, as follows. Medical devices that leach DEHP or other plasticizers shall include in a box a prominent, clearly-worded warning label stating:

i. the percentage of DEHP contained in the device, by weight;

ii. an estimate of the amount of leaching that can be expected to occur under routine usage and other anticipated usage circumstances;

iii. Appropriate information from the FDA Safety Assessment as to how the use may approach or exceed the tolerable intake;

iv. precautions that should be taken to reduce the potential for leaching of DEHP (e.g., guidelines for temperature of usage and storage, duration of usage); and

v. the following warning notice:

WARNING: The leaching of the plasticizer DEHP from this product may pose health hazards particularly when there is aggregate exposure

from multiple medical devices utilized by sensitive populations, such as [as appropriate to the product: in the care of women who are or may be pregnant, infants, patients undergoing ECMO, transfusion or cardiac bypass procedures or individuals receiving long term intravenous or tube-feeding treatment.] Alternative products that do not contain DEHP may be available as substitutes for this product. Consult the FDA periodical publication *FDA Consumer* or the FDA website www.fda.gov for additional information on alternatives.

4. 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. Clarify the scope and extent of the agency's proposed risk communication program and expand it to include communication on alternatives in addition to the hazards of DEHP, and include the petitioner in the development of the program.

5. Establish a program to expedite the development and usage of phthalate-free alternatives to PVC medical devices that leach plasticizers. This program may include the following actions:

a. Encourage FDA-regulated manufacturers to voluntarily shift to usage of materials without PVC and phthalate plasticizers ;

b. 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 plasticizers and any FDA-approved non-DEHP and non-PVC alternatives known to be available as substitutes.

STATEMENT OF GROUNDS

I. INFORMATION RELIED UPON IN THIS PETITION.

A. FDA Safety Assessment.

The FDA Reply states that:

In our two previous interim responses, we informed you that the FDA was conducting a safety assessment of the DEHP used in medical devices (12/2/99) and that because of the complexity and extent of the analysis, we anticipated that the agency's review would take several months (3/29/00). We have since completed the safety assessment and the internal review of this document. **The results of the safety assessment serve as the basis of the response to this petition.** [emphasis added]

Accordingly, because the FDA Safety Assessment[1] constitutes the rationale and a part of the factual record for the agency response to the petition, we rely on the Safety Assessment as well as other information submitted on the docket of this petition in our submittal for reconsideration.

B. Advamed and Baxter Studies.

HCWH has not seen and has been unable to obtain the entire "Advamed"[2] and "Baxter"[3] studies upon which the FDA, in part, bases its Safety Assessment. Concurrent with this petition for reconsideration, we are filing a separate Freedom of Information Act request for those studies. We note that neither study, to our knowledge, has been published in a peer reviewed journal, though FDA made prominent use of each in conducting the Safety Assessment of DEHP. Baxter officials claim that their study is publicly available, but HCWH has been unable to obtain a complete published version of the study. Advamed has refused to give us access to its study.[4] We reserve the right to

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[1] Center for Devices and Radiological Health, U.S. Food and Drug Administration, *Safety Assessment of Di(2-ethylhexyl)phthalate (DEHP) Released from PVC Medical Devices*, Sept. 6, 2001. (Hereafter, *"Safety Assessment"*).

[2] Cited in Safety Assessment as AdvaMed (2001) 21-Day repeat dose male reproductive tract study of di(2-ethylhexyl)phthalate (DEHP) administered either intravenously or orally to rats starting at neonatal age 3-5 days, with satellite recovery group through 90 days of age. Study number 11947.

[3] Cited in Safety Assessment as Baxter (2000) Histopathological evaluation of testes from neonatal male rats and rabbits treated with saline or approximately 62 mg/kg Di-(2-Ethylhexyl)Phthalate (DEHP) in 4% Bovine Serum Albumin (BSA) During Postnatal Days 3-21 (Rats) or 14-42 (Rabbits). Study number TP062830535.

[4] On Sept. 28, 2001, Julie Silas, Program Director for San Francisco Bay Area Physicians for Social Responsibility spoke with Tess Castle, "one of the principals working with the DEHP study at Advamed." Castle stated that "We are very pleased with the study and do want to make it available to the public. We need to wait until it is peer-reviewed." When asked about its reference in the FDA Safety Assessment she replied, "We did give a copy of the report to the FDA for their use in preparation for use in their 'risk assessment.' But to retain the integrity of the peer-review process, we cannot share it with the public at this time. It will be a couple of more months. We are not making it publicly available until it is published in a peer-review journal. It is always best to wait until it is published before public distribution" When asked what journal it will be published in, she responded, "I don't know the name of the publication, but I can call you with expected public release date."

comment additionally on the Safety Assessment, and to amend this petition, after we have seen the Advamed and Baxter studies.

II. DESCRIPTION OF THE FDA DECISION

The FDA states in its formal written reply that it has "denied" the HCWH petition. The FDA regulations on citizen petitions provide that the agency may "grant or deny... a petition in whole or in part, and may grant such other relief or take other action as the petition warrants." 21 CFR 10.30. While some of the statements in the Reply might be understood to be a "partial grant" of requests in the HCWH petition, and the facts and analysis of the Safety Assessment appear to necessitate a partial grant of the petition as a matter of law, the FDA Reply explicitly states that the petition is denied.

Moreover, the FDA Reply is not accompanied by the concrete, formal implementation actions that would be necessitated in a partial grant of the petition.

The agency states in its reply that it will be "implementing a risk communication strategy to notify health care providers of the results of the safety assessment." We believe this could be understood to constitute a partial grant of the request in the HCWH petition asking the agency to "Develop a market information and education program that informs health care providers of the hazards of PVC and DEHP and the availability of alternatives." The decision to engage in risk communication demonstrates the agency's agreement that this aspect of the petition merited an affirmative response; however, the lack of formal commitment to action by the FDA with the issuance of the reply -- for instance, the lack of delineation of this "risk communication strategy" means that the

agency has failed to comply with the duties of FDA regulations to take formal action consistent with the partial grant of a petition.

The FDA Reply also acknowledges substantial issues of concern to health of various patient populations, so that "risk reduction strategies are appropriate for some medical procedures that employ PVC devices." The Reply states that FDA will explore options to reduce exposure of some patient populations to DEHP. However, the FDA Reply stops short of taking formal action committing to initiating a proceeding for labeling or regulatory requirements for any product lines.

For instance, in the Safety Assessment, the FDA has acknowledged very substantial potential risks to neonates in neonatal intensive care units (NICU's), and an apparent need for risk reduction strategies:

> [N]eonates in the NICU environment are exposed to DEHP from multiple devices. Based on the dose of DEHP received in such procedures as intravenous administration of sedatives, administration of TPN and replacement transfusion, all common procedures in the NICU, it is possible to estimate that a 4 kg infant could receive a DEHP dose on the order of 3 mg/kg/day for a periods of weeks or months. The resulting TI/dose ratio in this setting is 0.2. In other words, the dose of DEHP received by some infants from device-related sources could be 5-fold greater than the TI. If the neonate is also undergoing ECMO treatment, the TI/dose ratio drops to around 0.05, indicating that the dose of DEHP received by some infants from device-related sources could be 20-fold greater than the dose of DEHP that is not expected to result in adverse effects following intravenous exposure.
>
> ...Accordingly, FDA/CDRH has examined this issue and has concluded that children undergoing certain medical procedures may represent a population at increased risk for the effects of DEHP. This decision is supported by three findings: 1) children undergoing some medical procedures receive a greater dose of DEHP, on a mg/kg basis, than adults do, 2) pharmacokinetic differences between children and adults may result in greater absorption of DEHP, greater conversion of DEHP to MEHP (the toxic metabolite of DEHP), and reduced excretion of MEHP in children compared to adults, and 3) children may be more pharmacodynamically sensitive to the adverse effects of DEHP than adults are. Safety Assessment, pages 6-7.

While the FDA acknowledges these very substantial potential risks to neonates, the FDA Reply fails to follow through with the necessary commitment to action to address the identified risks – e.g. initiating a rulemaking proceeding, or at least setting forth a schedule for action, including warning labels for this specific, admittedly high risk, population.

III. STATEMENT OF HEALTH CARE WITHOUT HARM'S INTEREST IN RECONSIDERATION AND CLARIFICATION.

Petitioner Health Care Without Harm, (HCWH), a coalition of health, religious, labor, and environmental organizations, hereby files this petition on behalf of its 335 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. The Center for Health, Environment and Justice is the primary fiscal sponsor for Health Care Without Harm. HCWH is located at 1755 S Street NW Unit 6B,Washington, DC 20009.

HCWH submits this petition:

-to ask the FDA to partially grant the citizens petition;

-to clarify and formalize the FDA's commitments to address each of the medical devices where the agency's Safety Assessment or other information before the

agency demonstrates a need to reduce exposures to DEHP from medical devices for adults, neonates or children;

-to preserve HCWH rights to enforce its June 1999 petition;

-to request disclosure and opportunity to comment on the proposed risk communication program on DEHP;

-to reserve the right of HCWH to comment on science issues in the Safety Assessment, and the implications they may have for the overall petition, until FDA disclosure and HCWH review of the Advamed and Baxter studies.

IV. THE FDA'S OWN ANALYSIS NECESSITATES LABELING AND OTHER ACTIONS.

A. The Safety Assessment identifies a number of uses and populations in which DEHP exposure from medical devices is projected to exceed tolerable intake levels.

The FDA Safety Assessment of DEHP provides a clear demonstration of the risks to patients justifying granting the petition in part. Page 47 of the Safety Assessment includes a table listing the FDA's estimates as to the likely level of DEHP exposure for neonates and adults in various medical applications and its relationship to the tolerable intake (TI/dose ratio). This chart shows that many contexts can involve uses that approach or exceed TI, in some cases exceeding the tolerable intake by as much as fifty times. We believe that any context that could approach the TI necessitates labeling in the absence of more stringent risk reduction measures that would eliminate the risk of such exposures. Since the FDA has so far not promulgated or even proposed further-reaching risk reduction measures, we demonstrate in this petition that as a matter of law the FDA is now required to promulgate labeling requirements. In the absence of labeling

Table *4-1*. Comparison of Tolerable Intake (TI) Values for DEHP to the dose of DEHP received by adult and neonatal patients undergoing various medical procedures.

	Adult		Neonate	
	DEHP dose (mg/kg/day)	TI/dose ratio	DEHP dose (mg/kg/day)	TI/dose ratio
Infusion of crystalloid IV solutions	.0005	120	.03	20
IV infusion of drugs requiring pharmaceutical vehicles for solubilization	0.15	4	0.03	20
TPN administration Without added lipid	0.03	20	0.03	20
With added lipid EVA bag with PVC tubing	0.13	5	2.5	0.2
	0.06	10		
Blood transfusion				
Trauma patient	8.5	*0.1*		
Transfusion/ECMO Pts.	3.0	0.2		
Exchange transfusion			22.6	0.02
Replacement transfusion Neonate in NICU			0.3	2
Replacement transfusion Correction of anemia in Patients receiving Chemotherapy and patients with sickle cell disease	0.09	7		
Replacement transfusion surgical patient undergoing CABG	0.28	2		
Treatment of clotting Disorders with Cryoprecipitate	0.03	20		
Cardiopulmonary bypass				
CABG	1	0.6		
Orthotopic heart transplant	0.3	2		
Artificial heart transplant	2.4	0.3		
ECMO			14	0.04
Apheresis	0.03	20		
Hemodialysis	0.36	2		
Peritoneal dialysis	<0.01	>60		
Enteral nutrition	0.14	0.3	0.14	0.3

Adult: 70 kg body weight Neonate: 4kg body weight
TI/Dose ratio based on TI of 0.6 mg/kg/day for parenteral exposures and 0.04 mg/kg/day for enteral nutrition.
SOURCE: Center for Devices and Radiological Health, U.S. Food and Drug Administration, *Safety Assessment of Di(2-ethylhexyl)phthalate (DEHP) Released from PVC Medical Devices*, Sept. 6, 2001, page 47.

specifically attached to or accompanying medical devices, nurses, doctors and other health care practitioners, and the patients themselves in some instances, will lack the information needed to prevent exposures approaching or exceeding the TI.

B. The Safety Assessment provides additional information demonstrating the need for labeling of other devices.

In addition, we note that the Safety Assessment contains information supporting the following specific medical devices and contexts in which there a need for labeling beyond the items approaching or exceeding TI in the above-referenced table.

1. Breast Feeding.

The Safety Assessment fails to develop a TI for women on dialysis who are breast feeding, even though they may transfer very high levels of DEHP to breast feeding infants:

> Based on theoretical estimates, it is possible for nursing infants of mothers on hemodialysis to receive very high doses of DEHP; however the exact dose received by these babies is highly uncertain. Because of the level of uncertainty in this estimate, a TI/Dose ratio was not derived for this means of exposure to DEHP. Also, because women on hemodialysis are typically infertile, the population of infants exposed in this manner is thought to be very small.

Although the women who are both receiving dialysis treatments and engaging in breast-feeding are a small population, the FDA often makes available and requires guidance for groups with relatively small numbers of individuals and about unlikely side effects that will only affect small populations (for example, when warning about uncommon adverse side effects of pharmaceuticals.) The agency should require guidance and documentation for dialysis related devices that specifically mentions this potential source of infant DEHP exposure.

of 3 when a no-observed-adverse-effect-level (NOAEL) is used to derive a TI, and 10 when a LOAEL is used to derive a TI. The assessment asserts that this accounts for the potential increased vulnerability of the fetus as compared to the neonate.

A UF3 of 3 (when a NOAEL is used to derive a TI) may not be adequately protective of the developing fetus. If, as Arcadi et al suggest, and as acknowledged by FDA on pg. 39, doses of DEHP an order of magnitude lower than those necessary to cause adverse effects in the neonatal period may harm the fetus, then a UF3 of 10 should be used to derive a TI based on either a NOAEL or LOAEL.

Beyond that, however, it remains important to recognize that the entire population is exposed to background levels of DEHP of approximately 3-30 micrograms/kg/day. (reference: NTP CERHR report). FDA cites Kohn et al who estimate maximal exposures to DEHP for women 20-40 yrs of age to be 10 microgms/kg/day. Inasmuch as most of this exposure is likely to be via the oral route, it follows that, at a background exposure level of 10 microgrms/kg/day, women of reproductive age are already exposed to 25% of the oral TI as calculated by FDA, and as much as 75% of the oral TI if background exposures are 30 microgm DEHP/kg/day, prior to any medical treatment. Consequently, when considering all sources of exposure, including those from background and medical treatment, pregnant women may easily exceed the TI.

According to the FDA Safety Assessment, patients receiving nutritional support with enteral feeding can receive a daily DEHP dose of about 0.14 mg/kg day, approximately 3.5 times the oral TI. It is reasonable to conclude from data cited by FDA that devices used in treating women who are pregnant or who may be pregnant that may result in an oral exposure to DEHP that may even approach the TI (like nasogastric tubes

carrying lipid-containing solutions, enteral feeding tubes and bags) should be labeled, as well as devices that will likely result in larger IV exposures like hemodialysis in pregnant women (though uncommon).

In addition, even the use of drug-delivery devices that leach DEHP can contribute incremental increases in DEHP, leading to cumulative prenatal exposure through IV's including in saline contexts. Although drugs may be accompanied by references to the need to avoid PVC/DEHP delivery devices, without corresponding warnings on the devices themselves health care providers may lack the necessary information to effectively avoid delivering cumulatively damaging doses of DEHP.

Aside from the question of whether the levels of prenatal DEHP exposure may reach the TI, a precautionary approach by the FDA would discourage fetal exposure to these materials at any level, especially when there may be safer alternatives available. Such an approach would be particularly appropriate because, as noted by FDA, the susceptibility of the developing fetus to toxic effects of DEHP may be substantially greater than that of the newborn infant.

3. Nutrition Products (TPN and Enteral Feeding).

The FDA Safety Assessment states that:

> Parenteral exposure to DEHP can occur following intravenous infusion of crystalloid solutions (e.g.,normal saline, D5W, Ringers Lactate) and drugs, administration of enteral nutrition and total parenteral nutrition (TPN) solutions, and transfusion of blood or blood products. In addition, patients undergoing cardiopulmonary bypass (CPB), extracorporeal membrane oxygenation (ECMO), hemodialysis or peritoneal dialysis can also be exposed to DEHP. The extent to which DEHP is released from PVC medical devices is largely a function of the lipophilicity of the fluid that comes into contact with the device. Substances like blood, plasma, red blood cell or platelet concentrates; IV lipid emulsion or total parenteral nutrition solution; and formulation aids (e.g., Polysorbate 80) used to

> solubilize IV medications can readily extract DEHP from PVC tubing and containers. In contrast, nonlipid-containing fluids, like crystalloid IV solutions, saline priming solution for ECMO and hemodialysis, and peritoneal dialysis solution, extract relatively small amounts of DEHP from the PVC constituents of the device.

While the Safety Assessment notes in the summary section that "non-PVC bags and tubing are typically used to administer TPN ... lessening the concern about DEHP-mediated effects," elsewhere the Assessment recognizes, in Annnex A, part A.1.2, that:

> PVC tubing and infusion pumps are always used to administer lipids to pediatric and neonatal patients.

Indeed, it is the case that DEHP-containing PVC tubing is often used to deliver parenteral and enteral nutritional formulas. Accordingly, these pediatric and neonatal patients face high exposures, which may be abated by the use of alternative materials. This presents an area of great need for labeling, to encourage a shift to alternative devices, many of which are already available.

With regard to adult TPN uses, where the FDA has noted a shift away from DEHP/PVC devices, it remains the case that there are many FDA-approved TPN delivery devices on the market that contain leachable DEHP.

Even though some lipid containing or lipophilic drugs or nutrition products may currently bear warnings against the use with PVC and DEHP products, effective labeling of bags and tubing is necessary in order to allow providers, pharmacists, home users, etc. to readily ensure that they are not using the devices which are cautioned against. Labeling of lipophilic drugs is insufficient without labeling the storage and administration products themselves (bags and tubing) to prevent these exposures.

For instance, the agency's Safety Assessment notes that there is generally low exposure to DEHP from bags containing saline solutions. But in the absence of labeling of the devices themselves, providers may not be aware that specific drugs are not supposed to be used with the PVC bag or tube in question. They may know that the drug warning says not to use it with devices containing PVC and DEHP, but may lack notice that the device contains the materials in question.

4. Additional Exposures to Patients Who May Already Be Exceeding the TI.

The Safety Assessment concludes (p. 46):

> DEHP dose estimates typically do not take into account exposure of patients to multiple PVC devices. Consequently, 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.

Adults, children and neonates undergoing medical procedures that according to the FDA Safety Assessment, may under some circumstances leach DEHP at levels approaching or in excess of tolerable intake may receive additional exposure from other medical devices. Health care providers cannot "assess" or act to limit "the potential risk of patients in various clinical scenarios" unless other medical devices with the potential to leach DEHP at any level are properly labeled.

5. Nonsystemic Effects.

The discussion of nonsystemic effects in Annex D of the Safety Assessment demonstrates a need to expand notices to consumers to encompass those additional hazards in products where they can arise. The Safety Assessment states, for instance:

> The conclusions reached in the safety assessment are based solely on the potential for DEHP to cause ... adverse systemic effects in exposed patients, based on TI values derived from animal studies. However, the clinical significance of various nonsystemic effects produced by DEHP is

> explored in Annex D. The ability of DEHP to alter the hemocompatibility of PVC tubing or result in adsorption of drugs to PVC tubing may be the most clinically important endpoints to consider in the risk management phase of the assessment, depending on the device.

The annex also mentions other issues with the use of DEHP, including "mediating drug adsorption onto PVC surfaces, and a possible role for DEHP in producing peritoneal sclerosis." The FDA labeling regulation on DEHP devices should take account of these risks, as identified in Annex D of the Safety Assessment.

V. THE FDA RISK COMMUNICATION STRATEGY IS INADEQUATELY DELINEATED.

The FDA Reply states that:

> FDA is implementing a risk communication strategy to notify health care providers of the results of the safety assessment, available via the FDA website. In addition, we have posted a Q & A document on the FDA webpage, "Consumer Update — DEHP in Plastic Medical Devices" that you may see at http://www.fda.gov/cdrh/ocd/dehp.html to communicate the risks of DEHP exposure from medical devices to health care providers and to the general public.

This statement could appear to be a partial grant of one request in the petition, which called for education of health care providers on DEHP in medical devices. But because it does not formalize or provide clarity about the kinds or range of activities the agency will utilize to notify providers of the substantial concerns identified in the Safety Assessment, the response falls short of a partial grant of the petition. The agency needs to identify the range of risk communication strategies that the agency is considering. In addition, HCWH requests that the FDA indicate how the petitioner and the public can provide input on those strategies. Moreover, to be effective in encouraging risk reduction, the risk communication strategy should also include information about the availability of

FDA-approved alternatives to DEHP leaching devices, as requested in the original petition.

In addition to its primary and statutorily mandated information-dissemination role in ensuring adequate product labeling, in recent years the FDA has engaged in more direct routes of communication and increased its communication with consumers and patients. According to a report from the FDA Task Force on Risk Management,[5] FDA outreach typically can include " press releases, talk papers, meeting announcements, safety alerts, public health advisories, articles, brochures, and medical bulletins." The agency's web site has also been used more extensively in recent years. The Center for Devices also routinely sends out a questionnaire concerning its safety alerts to a random sample of recipients to evaluate the effectiveness of prior communications. Such activities may be useful to the FDA in further getting the word out regarding the potential hazards posed by DEHP. The full scope of the FDA Risk Communication strategy awaits formalization, as required in a partial grant of the petition.

However, broad based risk communication on the Safety Assessment of DEHP in medical devices cannot *substitute for* product labeling to ensure effective provider decision making on the front lines of health care; instead, effective education and communication regarding the Safety Assessment is a helpful complement to an effective risk reduction strategy in which, by law, ensuring proper labeling is the keystone.

VI. LEGAL ANALYSIS

A. The FDA is required by law to require labeling of products presenting a potential hazard to health.

The FDA reply stated:

> In order to issue a regulation or guidance containing the labeling statement that you requested, FDA would need to determine that, without such a statement, the device would be misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 352)...
>
> Specifically, FDA would need to determine that the absence of such a statement would render the labeling of the device false or misleading or that, without such a statement, the labeling would not contain adequate directions for use of the device.

However, given the results of the Safety Assessment, the agency now has a legal mandate to require labeling, in the absence of other more stringent measures to phase out or restrict the use of DEHP, or to prevent potentially harmful levels of exposure in the numerous contexts of concern identified by the FDA. We elaborate on this mandate below.

By law, the primary method of communicating risk by the FDA is approved packaging and labeling. Not only is this the traditional method of FDA Risk Communication, it is the main method prescribed by statute. Where there are significant risks of usage that may cause potential injury to health, the requirement of ensuring adequate labeling is not optional, but is mandatory under FDA's statutory authority.

21 USC 352 provides various grounds on which a drug or device can be deemed

[5] TASK FORCE ON RISK MANAGEMENT, FDA, *CREATING A RISK MANAGEMENT FRAMEWORK: REPORT TO THE FDA COMMISSIONER*, Food and Drug Administration, May 1999.

to be misbranded and labeling required. Here are some of the germane ones that apply to this issue and brief analysis of their applicability:

> A product is considered misbranded "unless its labeling bears adequate directions for use." 21 USC 352 (f)(1)

Based on the Safety Assessment, many medical devices do not contain adequate directions for use because they may be utilized in a manner that can result in exposure to DEHP that endangers health. A label that would fail to warn a user against the use of the device in a manner that may approach or exceed the tolerable intake would meet this criterion.

> A device is also considered misbranded if it does not contain:
>
> (2) such adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users, except that where any requirement of clause (1) of this paragraph [labeling authority], as applied to any drug or device, is not necessary for the protection of the public health, the Secretary shall promulgate regulations exempting such drug or device from such requirement. 21 USC 352 (f)(2) [emphasis added]

The Safety Assessment has, in essence, stated that dosage, methods and duration of administration can result in levels of exposure dangerous to health and to children. By the above provisions of law it is not permissible for the FDA to ignore this unless it explicitly promulgates a regulation *exempting* these products from labeling requirements due to a lack of public health threat. Therefore, there is a clear mandate for the FDA to initiate a rulemaking on labeling -- either to require labeling of the products or to exempt these products from labeling if it has achieved other effective risk reduction

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http://www.fda.gov/oc/tfrm/Tableofcontents.htm

assurances. Under the terms of this provision the agency cannot escape its duty to require labeling without promulgating a regulation.

A product is also considered misbranded if it is:

> (j) Health-endangering when used as prescribed. If it is dangerous to health when used in the dosage or manner, or with the frequency or duration prescribed, recommended, or suggested in the labeling thereof, 21 USC 352 (j) [emphasis added]

The Safety Assessment has essentially affirmed that dosage or manner, or the frequency or duration prescribed, recommended, or suggested in the current labeling of products may be dangerous to the health of many patients. According to the FDA Safety Assessment, this is especially true for infants receiving multiple frequent prescribed treatments in a NICU environment.

In addition the law provides requirements for other statements in descriptive printed matter such as might apply to advertisements for nutritional or other products:

> (r) Restricted devices not carrying requisite accompanying statements in advertisements and other descriptive printed matter
>
> In the case of any restricted device distributed or offered for sale in any State, unless the manufacturer, packer, or distributor thereof includes in all advertisements and other descriptive printed matter issued or caused to be issued by the manufacturer, packer, or distributor with respect to that device (1) a true statement of the device's established name as defined in subsection (e) of this section, printed prominently and in type at least half as large as that used for any trade or brand name thereof, and (2) a brief statement of the intended uses of the device and relevant warnings, precautions, side effects, and contraindications and, in the case of specific devices made subject to a finding by the Secretary after notice and opportunity for comment that such action is necessary to protect the public health, a full description of the components of such device or the formula showing quantitatively

each ingredient of such device to the extent required in regulations which shall be issued by the Secretary after an opportunity for a hearing. 21 USC 352 (r)

B. FDA Guidance confirms the need for FDA to clarify labeling duties for DEHP products.

FDA guidance on device labeling provides that:

> "if the use of a device in a certain patient population is associated with a specific hazard, the hazard shall be described in the Precautions section, if appropriate the hazard shall be stated in the Warnings and the Contraindications section and the Precautions section of the labeling shall refer to it, e.g. "See the 'Warnings' section for information on..." FDA Device Labeling Guidance, G91-1, March 8, 1991.

This FDA guidance is intended primarily for use by FDA staff in premarket reviews; it is also intended for use by industry in preparing device labeling. Unfortunately, this guidance does not make it clear how devices containing DEHP should be handled in light of the findings of the FDA Safety Assessment, nor does the safety assessment make it clear when labeling will be required as a result of the agency's findings. As a next step, the agency might declare in a guidance or regulation that its Safety Assessment has identified specific hazards meriting specific precautions, for instance. In any event, based on the complex findings of the Safety Assessment, a more specific guidance or regulation is necessary to clarify when labeling is required.

C. The FDA is required by its citizen petition regulations to undertake formal implementation actions when it responds affirmatively to a petition.

The above discussion demonstrates the need for affirmative responses by the FDA, granting the HCWH petition in part. In so doing, the agency is obliged by its own regulations to make a more formal commitment to action than it has done to date. Under FDA regulations on citizen petitions, if the agency approves a petition in whole or part,

"the Commissioner shall concurrently take appropriate action (e.g., publication of a FEDERAL REGISTER notice) implementing the approval." 21 CFR 10.30(e) (2). Clearly this regulation contemplates a more formal commitment to action than that emerging from the FDA Reply.

Even if the FDA Reply as written were intended to be a "partial grant" of the HCWH petition, the absence of specific risk reduction and labeling actions would negate the effectiveness of such grant. More formal action is necessary.

VII. ACTIONS REQUESTED.

We hereby petition the FDA to reconsider its reply to the HCWH petition and to take the following actions:

1. Grant the petition in part;

2. As required by FDA regulations on citizen petitions, take formal action to implement responsive action, including identifying the agency's commitments including timelines, benchmarks, medical devices and areas of utilization targeted, etc.;

3. Initiate rulemaking or issue a guidance consistently requiring labeling of:

   a. 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; 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;

b. All PVC medical devices that may pose, when used by pregnant or potentially pregnant women, prenatal exposures to DEHP at any level;

c. All PVC medical devices that may be utilized in conjunction with Breast Pumps and Breast Milk and leach DEHP into the breast milk;

d. 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;

e. All PVC medical devices that may leach DEHP when used intentionally or inadvertently with lipid-containing nutrition or lipophilic drugs;

f. All PVC medical devices that may leach DEHP that could add to the DEHP exposure of patients that are also undergoing a medical procedure that, according to the FDA Safety Assessment, may under some circumstances leach DEHP at levels approaching or in excess of tolerable intake; and

g. All medical devices that may cause nonsystemic effects as indicated in Annex D of the FDA Safety Assessment of DEHP medical devices.

In each of these contexts, include prominent, clearly worded labeling as to the potential for DEHP or other phthalates to leach, and the potential for health effects from exposure to DEHP, as follows. Medical devices that leach DEHP shall include in a box a prominent, clearly-worded warning label stating:

i. the percentage of DEHP contained in the device, by weight;

ii. an estimate of the amount of leaching that can be expected to occur under routine usage and other anticipated usage circumstances;

iii. Appropriate information from the FDA Safety Assessment as to how the use may approach or exceed the tolerable intake;

iv. precautions that should be taken to reduce the potential for leaching of DEHP (e.g., guidelines for temperature of usage and storage, duration of usage); and

v. the following warning notice:

WARNING: The leaching of the plasticizer DEHP from this product may pose health hazards particularly when there is aggregate exposure from multiple medical devices utilized by sensitive populations , such as [as appropriate to the product: in the care of women who are or may

be pregnant, infants, patients undergoing ECMO, transfusion or cardiac bypass procedures or individuals receiving long term intravenous or tube-feeding treatment.] Alternative products that do not contain DEHP may be available as substitutes for this product. Consult the FDA periodical publication *FDA Consumer* or the FDA website www.fda.gov for additional information on alternatives.

4. 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. Clarify the scope and extent of the agency's proposed risk communication program and expand it to include communication on alternatives in addition to the hazards of DEHP, and include the petitioner in the development of the program.

5. Establish a program to expedite the development and usage of phthalate-free alternatives to PVC medical devices that leach plasticizers. This program may include the following actions:

a. Encourage FDA-regulated manufacturers to voluntarily shift to usage of materials without PVC and phthalate plasticizers ;

b. 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 plasticizers and any FDA-approved non-DEHP and non-PVC alternatives known to be available as substitutes.

Petitioners request that the agency provide an answer to this petition for reconsideration within 60 days of this submittal.

Respectfully submitted,

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October 4, 2001

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