DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JUN 19 2003

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Marcus Schabacker, MD, Ph.D.
B. Braun Medical Inc.
824 Twelfth Avenue
Bethlehem, PA 18018-0027

Re: Docket No. 02P-0450/CP1

Dear Dr. Schabacker:

This letter responds to your citizen petition dated October 15, 2002, requesting that the Food and Drug Administration (FDA) withhold approval of any and all pending or future abbreviated new drug applications (ANDAs) for amino acid solutions packaged in di(2-ethylhexyl)phthalate (DEHP)-plasticized polyvinyl chloride (PVC) and intended for use in infant patient populations. The request is based on concerns that the potential leaching of DEHP may have harmful toxic effects on the human body, especially infants. In making our decision, we have considered the information in your petition, your supplement to the petition, comments to your petition submitted by Baxter Healthcare Corporation (Baxter),[1] the specific product for which Baxter has submitted an ANDA that you request FDA not approve, and other information available to the Agency. This letter addresses only the issues you raise specifically related to the product PremaSol. Although FDA will continue to assess the potential risk of exposure to DEHP from various sources, for the reasons stated below, your petition is denied.

I. BACKGROUND

B. Braun Medical Inc. (B. Braun) is the sponsor of TrophAmine (NDA 19-018), a 6% and 10% amino acid solution indicated for neonatal nutritional therapy. Baxter has a pending ANDA for PremaSol, the generic version of TrophAmine. The primary difference between PremaSol and TrophAmine is the containers.[2] TrophAmine is packaged in sterile 500 mL glass containers, and contains sodium metabisulfite as an antioxidant. PremaSol is dispensed in Viaflex PL-146 bags manufactured from DEHP-plasticized PVC. DEHP is commonly used to reduce the brittleness of PVC.

[1] In a letter dated December 2, 2002, Baxter submitted comments on the petition. In a letter dated April 3, 2003, you submitted a supplement in further support of your citizen petition.
[2] Baxter filed a suitability petition because the container size of its generic product differed from the reference listed product. We approved Baxter's suitability petition on January 11, 2001.

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Both products are designed to be a primary component of total parenteral nutritional therapy (TPN) in infants and young children. Amino acid infusions improve nitrogen balance, serum protein concentration, and weight gain. Other components of TPN not supplied by TrophAmine or PremaSol include cysteine hydrochloride, dextrose (as a calorie source), electrolytes, vitamins and minerals, and a source of essential fatty acids.

II. DISCUSSION

In your petition, you request that FDA withhold approval of any and all pending or future ANDAs for amino acid solutions that are packaged in DEHP-plasticized PVC and are intended for use in infant patient populations. You specifically request that FDA not approve the ANDA that has been submitted for PremaSol. You base this request on the claim that animal toxicity data suggest that there may be long-term toxicity from DEHP exposure, and that the DEHP exposure from PremaSol exceeds the recommended exposure (tolerable intake (TI)) for pediatric patients. (Petition at 4 and 6-7.)

Much of the support you cite for your citizen petition comes from three FDA documents indicating that exposure to DEHP may have toxic effects on the human body and that DEHP leaches into solutions that come into contact with DEHP-plasticized PVC containers: (1) *Safety Assessment of di(2-ethylhexyl)phthalate (DEHP) Released from PVC Medical Devices* (Safety Assessment), available at http://www.fda.gov/cdrh/ost/dehp-pvc.pdf;[3] (2) the FDA draft guidance for industry, *Medical Devices Made with Polyvinyl Chloride (PVC) Using the Plasticizer di(2-Ethylhexyl)phthalate (DEHP)* (DEHP Guidance), available at www.fda.gov/cdrh/ode/guidance/1407.html; and (3) FDA's public health notification summarizing the Safety Assessment, *FDA Public Health Notification: PVC Devices Containing the Plasticizer DEHP* (Health Notification), available at http://www.fda.gov/cdrh/safety/dehp.html.

A. PVC and DEHP in Medical Devices

PVC is a rigid plastic polymer commonly used to manufacture medical devices such as intravenous (IV) tubing and bags for IV solutions, blood, and blood products. DEHP is a phthalate ester, is lipophilic with poor water solubility, and is commonly added as a plasticizer to the PVC used in medical devices. In these devices, DEHP is not chemically bound to the PVC, but is attached to the

[3] CDRH conducted the Safety Assessment to provide risk managers with information necessary for informed regulatory decision-making regarding the safety of DEHP released from medical devices. The Safety Assessment noted that the ability of DEHP to produce adverse effects in humans has been the topic of active discussion and debate in the scientific and regulatory communities. CDER characterized its approach in the Safety Assessment as health protective or conservative since worst-case scenarios were used to be protective of sensitive population groups. The Safety Assessment distinguished among the risks posed by patient exposure based on the type of medical procedure involved.

PVC matrix in a semi-solid or gel-like complex.[4] DEHP confers valuable qualities to medical devices made of PVC. These qualities include flexibility, strength, suitability for use in a wide variety of temperatures and for sterilization processes, optical clarity, and resistance to kinking and leaking.

Leaching of DEHP from a plastic bag into the stored solutions is dependent primarily on the chemical and physical properties of the solution. Large amounts of DEHP may leach into lipophilic solutions and biological products (such as whole blood, packed red blood cells, and plasma), whereas little to no DEHP leaches into colloid and crystalloid solutions . (See CERHR Evaluation.) TPN formulations contain amino acids, dextrose, electrolytes, and lipids. The addition of lipids will increase the extraction of DEHP from PVC bags, whereas little to no DEHP leaches from PVC bags containing nonlipid TPN solutions. (See Safety Assessment.)

Mono (2-ethylhexyl)-phthalate (MEHP) is the primary metabolite of DEHP and is believed to be the source of most toxicity from DEHP exposure. (See Safety Assessment) MEHP is always found in combination with DEHP, although at much lower concentrations. MEHP production is greater with oral exposure than with IV exposure to DEHP because the enzyme lipase, found in high concentrations in the mucosa of the gastrointestinal tract, catalyzes the conversion of DEHP to MEHP. As a result, the TI exposure limits for DEHP taken orally are lower than those for IV intake.

B. DEHP Toxicity

In the petition, you voice your concern about the safety of administering an amino acid solution from a DEHP-containing IV container to infant populations. You rely upon several documents published by the Agency indicating that infants undergoing certain medical procedures may represent a population at increased risk when exposed to DEHP. You point out that the FDA Health Notification states that DEHP can leach out of plastic medical devices into solutions that come in contact with the plastic and that the amount of DEHP that leaches out depends on the duration of contact with the plastic. (Petition at 4.) You note that the Health Notification also states:

> Exposure to DEHP has produced a range of adverse effects in laboratory animals, but of greatest concern are effects on the development of the male reproductive system and production of normal sperm in young animals. . . .[I]n view of the available animal data, precautions should be taken to limit the exposure of the developing male to DEHP. (Petition at 4.)

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[4] Center for Evaluation of Risks to Human Reproduction (2000) *CERHR Evaluation of DI (2-ETHYLHEXYL) PHTHALATE* (CERHR Evaluation), *Final Draft,* available at http://cerhr.niehs.nih.gov/news/DEHP-final.pdf

In addition, you mention that the FDA has identified several procedures, including TPN, as high risk because they could expose neonates to DEHP. (See Health Notification; Petition at 4.) Since the neonatal population possesses a heightened sensitivity to DEHP, you claim that the Agency suggests that reducing potential DEHP exposure associated with certain neonatal intensive care unit procedures (including bags used to store and transport TPN) should be a primary focus for Agency and industry. (See DEHP Guidance; Petition at 5.)

Although animal studies have indicated adverse events due to DEHP exposure,[5] the Agency is not aware of any reports of such adverse events in humans.[6] DEHP toxicity studies have found IV and oral exposure to be associated with testicular toxicity in rats, mice, guinea pigs, and ferrets, but not in higher order primates such as young adult marmosets and cynomolgus monkeys. (See CERHR Evaluation.) Lower order mammals, such as rats and mice, have much higher concentrations of gastric mucosa lipases (lipase catalyzes the conversion of DEHP to the toxic metabolite MEHP) than higher order mammals such as primates. This could explain the observed inter-species variation in DEHP toxicity. Consistent evidence from a large body of animal and developmental toxicology studies indicate that exposure to high levels of DEHP may be toxic to developing animals and, by inference, young infants. However, inconsistencies in the animal literature across species make it difficult to draw firm inferences from the animal toxicological literature to humans.

With respect to the leaching of DEHP, the complete text from the Health Notification reads as follows:

> DEHP can leach out of plastic medical devices into solutions that come in contact with the plastic. The amount of DEHP that leaches out depends on the temperature, *the lipid content of the liquid*, and the duration of contact with the plastic. (Emphasis added.)

In addition, the Safety Assessment states:

> 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 cells 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

[5] Such studies have shown that the primary organ targets for DEHP toxicity are the liver (in which exposure causes hepatomegaly and other effects in some but not all species) and the testicle. (See Safety Assessment.)

[6] See Health Notification. It should be noted that no human studies have explored whether human exposure to DEHP by any route is associated with testicular or other organ toxicity because conducting such studies would be methodologically difficult.

> solution for ECMO and hemodialysis, and peritoneal dialysis solution, extract relatively small amounts of DEHP from the PVC constituents of the device.

The amino acid preparation that is the subject of the ANDA does not contain lipids and, therefore, would be expected to leach very small amounts of the plasticizer from DEHP-plasticized PVC bags or tubing. Furthermore, your assertion that FDA has identified TPN as one of the highest risk procedures is only partially accurate. The Health Notification clearly indicates that concern over DEHP exposure from TPN in neonates is a high-risk procedure *when the PVC bag contains lipids*. Consequently, we disagree with your conclusions on DEHP toxicity in infant populations that might result from the use of PremaSol. We recognize the possible significance of the animal study results regarding DEHP exposure. Therefore, we have addressed the concern of DEHP exposure to lipid products in the DESCRIPTION and the DOSAGE AND ADMINISTRATION sections of the PremaSol labeling as follows:[7]

> Intravenous fat emulsion should not be administered in polyvinyl chloride (PVC) containers that use di-2-ethylhexyl phthalate (DEHP) as a plasticizer, because the fat emulsion facilitates the leaching of DEHP from these containers.

The risk of exposure is also reduced because PremaSol is intended for use in the preparation of admixtures for IV infusion, is not intended for direct administration to the patient, and is typically mixed in another, separate container with other products prior to administration to the patient.

C. DEHP Exposure - Tolerable Intake Level

You assert that the DEHP exposure from PremaSol exceeds the recommended exposure for pediatric patients. (Petition at 5.) You claim the Safety Assessment states that the TI established for adults for parenteral exposure (0.6 mg/kg/day) is not applicable to the pediatric population. (Petition at 5.) You assert that the limit of 0.6 mg/kg/day is too high for pediatric patients because the majority of DEHP is metabolized through glucuronidation and pediatric patients have a reduced capacity to metabolize compounds by this method (Petition at 6.) In addition, you mention that pediatric patients are more sensitive because they have undeveloped organs, such as testes, and, on the basis of weight, have greater exposure to DEHP toxicity when provided with the same dose as an adult. (Petition at 6). Finally, you state that FDA did not determine a separate TI for pediatric patients, even though pediatric patients

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[7] Drug labeling for approved ANDAs can contain differences from the reference listed drug when the differences relate to the packaging of a drug product. See section 505(j)(2)(A)(v) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355 (j)(2)(A)(v)); 21 CFR 314.94(a)(8)(iv); *Zeneca, Inc. v. Shalala*, 213 F.3d 161 (4th Cir. 2000).

may be much more susceptible to the toxic effects of DEHP exposure. (Petition at 6.)

The parenteral TI in the Safety Assessment explicitly took into account the potential for critically ill neonates to be at increased risk for the adverse effects of DEHP, compared with healthy adult populations. The Agency considered the reduced ability of neonates to metabolize DEHP through glucuronidation and the potential for testicular tissue to be more sensitive to the effects of DEHP in neonates than in post-pubertal children and adults. As a result, the TI was derived to be protective for all exposed patient populations, including male neonates.

You estimate the exposure amount for a neonate being administered TPN using solutions from PVC containers plasticized with DEHP. (Petition at 6.) You state that the labeled limit for DEHP in PVC IV bags, such as Baxter's PL-146 PVC IV bag, is 5 ppm (otherwise stated as 5 micrograms (μg)/mL or 5 mg/L). (Petition at 6.) You calculate that the doses for a 1 kg and 2 kg NICU infant in a neonate intensive care unit are 144% and 72% of the parenteral TI, respectively.

You overestimated the potential DEHP exposure from the PremaSol product by a factor of 25. Your calculations were based on a DEHP specification of 5 ppm, but the regulatory limit for DEHP in this product is 0.2 ppm (or 0.0002 mg/mL). Baxter has provided adequate stability testing to demonstrate that their product meets its established specifications. At this very low DEHP concentration, a 1.0 kg infant would have to receive at least 3000 ml per day of crystalloid before reaching the daily parenteral TI of 0.6 mg DEHP/kg/day. However, the daily fluid intake recommendation for infants weighing 10 kg or less is 100 to 125 cc/kg/day—a fluid intake level twenty four to thirty times lower than the intake required to reach the TI for DEHP.

Applying the current FDA TI for DEHP and this level of leaching for DEHP, PremaSol stored in Viaflex PL 146 containers does not pose a hazard to newborns, including neonates. As a result, we disagree with your claims regarding DEHP exposure and TI levels.

Finally, you assert that to identify the TI value for adults with DEHP exposure, FDA inappropriately rejected a published long-term study by Jacobson et al.,[8] in favor of two unpublished short-term studies by Baxter (2000) and AdvaMed (2001). We disagree. The Safety Assessment (at 24) clearly states the rationale for not using the results of the Jacobson study as the basis for the TI values for DEHP. The Agency rejected this study after performing an extensive review of the published literature on DEHP. We also noted in the Safety Assessment that

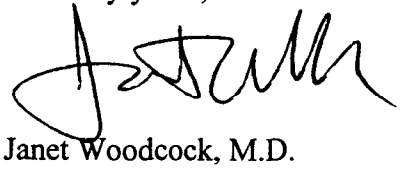
[8] Jacobson, M.S., Kevy, S.V., and Grand, R.J. (1997). Effects of plasticizer leached from PVC on the subhuman primate: a consequence of chronic transfusion therapy. *J Lab Clin Med*, 89: 1066-1079.

our decision was consistent with that of other regulatory agencies and advisory panels.

III. CONCLUSION

The Agency is aware of the potential risk for infant patient populations resulting from the exposure to DEHP, but the information presented in your petition on DEHP toxicity and exposure levels does not demonstrate that PremaSol poses a safety risk. Furthermore, language is included in the PremaSol labeling to help protect infant patients from potential exposure to DEHP. Therefore, we are denying your request to withhold approval of any and all pending or future ANDAs for amino acid solutions packaged in DEHP-plasticized PVC and intended for use in infant patient populations, including the ANDA for PremaSol. We recognize your concerns and we will continue to consider the issue of DEHP exposure, where appropriate, when reviewing product applications.

Sincerely yours,



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