



6005

Marcus Schabacker, MD, PhD
Corporate Vice President
R&D, Medical & Clinical Affairs

VIA FEDERAL EXPRESS

B. Braun Medical Inc.
824 Twelfth Avenue
Bethlehem, PA 18018-0027
Telephone: (610) 997-4475
Fax: (610) 691-6651

October 15, 2002

Dockets Management Branch (HFA-305)
Food and Drug Administration
Department of Health and Human Services
Room 10-61
5630 Fishers Lane
Rockville, MD 20857

CITIZEN PETITION

B. Braun Medical Inc. (B. Braun) hereby submits this Citizen Petition under Section 505(j) of the Federal Food, Drug and Cosmetic Act (FDC Act) and pursuant to 21 C.F.R. §§10.20 and 10.30. The purpose of this petition is to request that the Food and Drug Administration withhold approval of any Abbreviated New Drug Application (ANDA) for amino acid solution drug products intended for use in infant patient populations which are packaged in polyvinyl chloride (PVC) containers that have been plasticized with di(2-ethylhexyl)phthalate (DEHP). B. Braun makes this request following FDA's release of its own information documenting DEHP toxicity in this sensitive patient population.

A. Action Requested

B. Braun respectfully requests FDA withhold approval of any and all pending or future ANDAs for amino acid solutions packaged in DEHP-plasticized PVC and that are intended for use in infant patient populations.

02P-0450

CPI

B. Statement of Grounds

1. Background

B. Braun is the sponsor of approved NDA 19-018 for TrophAmine®. TrophAmine® (6% and 10% Amino Acid Injections), intended for neonatal nutrition therapy. TrophAmine® is packaged in glass containers.

B. Braun is aware of one pending ANDA for a generic version of TrophAmine®, to be packaged in PVC containers that have been plasticized with DEHP. This ANDA was publicly disclosed by its sponsor, Baxter Healthcare Corporation (Baxter) in an ANDA suitability petition submitted under § 505(j)(2)(C) of the FDC Act (Docket No. 00P-1470; Exhibit A). Baxter's petition discloses that, after ANDA 75-880 was submitted, the Office of Generic Drugs asked Baxter to file an ANDA suitability petition because some of its proposed container sizes are larger than the container sizes for TrophAmine®. By letter dated January 11, 2001, FDA approved Baxter's suitability petition (Exhibit B).

Baxter's petition clearly discloses that its proposed product will be packaged in its PL 146® plastic containers. Baxter's PL 146® plastic containers are manufactured from DEHP-plasticized PVC. See discussion in 2.a below and Exhibit C, page 12.

2. The Toxicity of DEHP

B. Braun relies upon safety information and alerts published by FDA indicating that exposure to DEHP has harmful toxic effects on the human body, that infants are especially at risk if exposed to DEHP, and that DEHP leaches into solutions that come into contact with DEHP-plasticized PVC containers creating the risk of DEHP exposure. In light of this information, B.Braun

is concerned about the safety of administering an amino acid solution from a DEHP-containing intravenous (IV) container, to infant populations which FDA's publications indicate to be at high risk of exposure to DEHP.

A summary of the relevant FDA publications follows:

- a. Safety Assessment of Di(2-ethylhexyl)phthalate (DEHP)
Release from PVC Medical Devices,
Center for Devices and Radiological Health,
Food and Drug Administration 2001 (Exhibit C)

In this Safety Assessment, FDA cites toxic effects of DEHP, and specifically addresses the health risks associated with exposing infants to DEHP. The assessment identifies children as a population of particular DEHP sensitivity. Page 6.

The Safety Assessment also notes that one route of possible DEHP exposure is where DEHP leaches out of plastic medical devices into solutions that come into contact with the plastic. The agency notes that the amount of DEHP that leaches out depends on the duration of contact with the plastic. Page 13. Furthermore, the FDA identifies IV bags as one of the devices known to FDA to leach DEHP. Page 10. Baxter's PL 146® bags are identified as a source of DEHP. Page 12.

- b. FDA Public Health Notification: PVC Devices Containing The Plasticizer DEHP
Center For Devices And Radiological Health
Food And Drug Administration, July 12, 2002 (Exhibit D)

FDA's Public Health Notification is a summary of its September 2001 Safety Assessment (item a. above). This document notes and reiterates the concerns stated in the Safety Assessment but in a format that is less technical and intended by the agency to be distributed among health care professionals in order to raise awareness of the issue.

In making its points FDA states that “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.”

Regarding routes of DEHP exposure, FDA states that “DEHP can leach out of plastic medical devices into solutions that come into contact with the plastic” and that “the amount of DEHP that will leach out depends on the duration of contact with the plastic”. The document goes on to say that seriously ill individuals (who often require several procedures using PVC devices) are exposed to higher levels of DEHP.

In addition, this document also provides a list of “Highest risk procedures” identified by FDA for DEHP exposure. This list includes several procedures which could expose a neonate to DEHP and recommends that health care professionals avoid use of devices containing DEHP-plasticized PVC when performing these identified procedures because of the associated health risk. Included among the procedures identified by FDA is total parenteral nutrition (TPN). TPN is the intended use for Baxter’s proposed PremaSol, packaged in DEHP-plasticized PVC.

- c. Medical Devices Made With Polyvinyl Chloride (PVC) Using The Plasticizer di-(2-Ethylhexyl)phthalate (DEHP): Draft Guidance For Industry And FDA U.S. Department of Health and Human Services, Food and Drug Administration, Center for Devices And Radiological Health, Office of Device Evaluation, September 6, 2002 (Exhibit E)

This draft guidance is aimed at manufacturers of products containing DEHP-plasticized PVC and highlights the agency’s health concerns regarding DEHP. The document also points out that FDA considers the neonatal population as one that possesses a heightened sensitivity to DEHP and

that devices used in Neonatal Intensive Care Units (NICU) may expose this population to levels of DEHP significant enough to cause concern over the possible adverse health effects. Page 2. Therefore, FDA suggests that DEHP-plasticized PVC products associated with these procedures (including bags used to store and transport TPN formulae like TrophAmine®) should be a primary focus for the agency and industry efforts to reduce potential DEHP exposure. Page 2. FDA suggests that the industry “consider all mechanisms to reduce patient exposure to DEHP” including “eliminating the use of DEHP in certain devices that can result in high aggregate exposures in sensitive patient populations.” Page 1.

3. The Proposed Product In DEHP-Plasticized PVC Is Not Safe For The Intended Population

a. The DEHP Exposure From This Product Exceeds Recommended Exposure For Pediatric Patients

The FDA Safety Assessment explicitly “concluded that children undergoing certain medical procedures may represent a population at increased risk for the effects of DEHP.” Exhibit C at page 6. Thus, while the tolerable intake (TI) established for adults for parenteral exposure was 0.6 mg/kg/day, Exhibit C at pages 4 and 43, this limit is not applicable to the pediatric population.¹

¹ As noted below, we also believe that the unbiased long term data (study by Jacobson, et al., (1977), discussed in Exhibit C at page 24) clearly substantiate a TI for adults that is most likely an order of magnitude lower than the TI set forth in the assessment (0.4 mg/kg/day).

For instance, “children have a reduced capacity to metabolize compounds via gluconidation, compared to adults.” Exhibit C at page 32. Since the majority of DEHP is metabolized by this method, it is quite clear that the limit of 0.6 mg/kg/day is simply too high for children. There are other reasons why children are more sensitive, including the fact that children have undeveloped organs, such as testes, which are the target of toxicity and are in a more susceptible state in infancy. Moreover, on a per weight basis, children have greater exposure to DEHP toxicity when provided with the same dose as an adult. Finally, children receiving parenteral nutrition represent a high risk subset within a high risk pediatric population. This “[a]ltered health status may potentiate DEHP effects on organs.” Exhibit C at page 33.

Moreover, FDA did not determine a separate TI for pediatric patients, even though children may be much more susceptible to the toxic effects of DEHP exposure. Exhibit C at page 32. FDA’s Safety Assessment concludes that an infant receiving TPN using PVC tubing could receive approximately 10 mg of DEHP per day (2.5 mg/kg/day for a 4 kg neonate). Exhibit C at pages 13 and Annex A, ninth unnumbered page. At this dose, the adult parenteral TI of 0.6 mg/kg/day (Exhibit C at pages 4 and 43) would be exceeded by a factor of four. It follows that the dose on a mg/kg body weight basis will be even higher for a typical 1-2 kg premature infant in the NICU.

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 µg/mL or 5 mg/L). Exhibit C, Annex A at third and fourth unnumbered pages. If this limit is used in the calculation of the pediatric exposure to DEHP from a hypothetical 150 mL daily dose of TPN, the daily dose of DEHP is 816 µg (150 mL x 5 µg/mL) + 116 µg (for DEHP

from tubing) = 866 µg).² For a 1 kg and 2 kg NICU infant, these doses are 144% and 72% of the parenteral TI, respectively. See Exhibit C at page 43.

Clearly, pediatric patients undergoing TPN using solutions from PVC containers plasticized with DEHP will be at a significant risk for injury. We simply do not believe that, in the absence of any compelling necessity, any DEHP-containing product should be approved for use in neonatal or infant population where a comparable or equivalent non-DEHP containing product is available. There is simply no credible rationale to justify such risk.

b. The Tolerable Intake Identified For Adult Patients Did Not Consider The Only Long-Term Study of Exposure to DEHP and, Therefore, Set a Tolerable Limit That Was Too High

The FDA Safety Assessment identifies a TI value for adults with exposure to DEHP. However, in so doing, FDA rejected a published long-term study by Jacobson et al (1977), in favor of two unpublished short-term studies by Baxter Corporation (2000) and AdvaMed (2001). Exhibit C, at pages 24 and 29. We do not believe that approach was appropriate for two independent reasons.

First, by its very nature, the long term study clearly yielded more reliable information than the short term studies. Second, the short-term Baxter and AdvaMed studies are of limited credibility due to the fact that they were produced by manufacturers of products containing DEHP with a financial interest in the outcome of the data. On the other hand, the long-term Jacobson study was

² (Dosage volume x DEHP exposure) + DEHP exposure from PVC tubing [116 µg, Exhibit C at page 12] = total DEHP exposure. For 150mL dose See Exhibit C, Annex A at ninth unnumbered page.

produced by independent scientists with no such disqualifying interests. Had the agency properly considered the lowest observed adverse effect-level presented in the Jacobson study, we believe the agency would have established a TI significantly lower than the one it used. See Exhibit C at pages 21 and 22.

4. Legal Authority

Under Section 505(j)(4)(A) of the FDC Act, FDA may not approve an ANDA if it concludes that “the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity.” In the matter at hand, the agency has time and again noted the potential health risks associated with the use of DEHP-plasticized PVC containers in infant patient populations. Therefore, under section 505(j)(4)(A) of the FDC Act, FDA should not approve any ANDA seeking approval for amino acid solutions which are packaged in containers made of DEHP-plasticized PVC products.

C. Environmental Impact

Under 21 C.F.R. Part 25, the undersigned claims exclusion from the preparation of an environmental assessment.

D. Economic Impact

Pursuant to 21 C.F.R. § 10.30(b), B. Braun will submit an economic impact statement upon the request of the Commissioner.

E. 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 and information known to the Petitioner which are unfavorable to the Petition.

Respectfully submitted,



Marcus Schabacker, MD, Ph.D.

cc: Ms. Helen Winkle
Acting Director, Office of Pharmaceutical Science
Center for Drug Evaluation and Research

Mr. Gary J. Buehler
Director, Office of Generic Drugs
Center for Drug Evaluation and Research

Frank O. Holcombe, Jr., Ph.D.
Associate Director for Chemistry
Office of Generic Drugs
Center for Drug Evaluation and Research