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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

**Re: Docket No. 02P-0450 B. Braun Petition – Withhold Approval for
Amino Acid Solution Drug Products – Comments and Request for
Denial**

Dear Sir or Madam:

We respectfully submit the following comments in opposition to the above referenced citizen's petition. B. Braun's petition requests that FDA withhold approval of any and all pending or future ANDAs for amino acid solutions packaged in DEHP-plasticized PVC that are intended for use in infant patient populations. B. Braun is the sponsor of approved NDA 19-018 for TrophAmine[®] (6% and 10% Amino Acid Injections), intended for neonatal nutrition therapy and packaged in glass containers. The B. Braun petition cites the August 9, 2000 ANDA Suitability Petition submitted by Baxter Healthcare Corporation ("Baxter") regarding a generic version of B. Braun's TrophAmine[®] product. B. Braun's citizen petition notes that the Premasol[™] solution described in the Baxter's ANDA suitability petition is packaged in Viaflex[®] PL 146[®] containers which are manufactured from DEHP-plasticized PVC.

We conclude based on FDA's DEHP risk assessment and the potential DEHP exposure from the crystalloid Premasol[™] product described in the ANDA Suitability Petition, that the B. Braun petition has no scientific merit and that the action requested should be denied for the following reasons:

1. The B. Braun petition misrepresents FDA's own Safety Assessment and incorrectly alleges a safety concern with crystalline amino acid solutions packaged in DEHP-plasticized PVC containers.

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B. Braun's petition relies upon safety information and alerts published by FDA on DEHP including "Safety Assessment of Di(2-ethylhexyl) phthalate (DEHP) Release from PVC Medical Devices" (Attachment 1) and "FDA Public Health Notification: PVC Devices Containing the Plasticizer DEHP" (Attachment 2). The FDA Safety Assessment specifically encompassed crystalline IV solutions packaged in DEHP-plasticized containers for neonatal patients. In the Safety Assessment, FDA concludes:

"There is little to no risk posed by patient exposure to the amount of DEHP released from PVC IV bags following infusion of crystalloid fluids" (Attachment 1, pg.5, 10-11). FDA's Safety Assessment also states "neonates receiving TPN (total parenteral nutrition) with lipid may be at increased risk of DEHP-mediated adverse effects" (Attachment 1, pg.5). However, FDA concludes, "in the absence of lipid-containing substances, the amount of DEHP that leaches from PVC storage bags into crystalloid IV solutions is generally very small." (Attachment 1, pg.12). The estimated upper bound dose for neonates (4kg) is 0.03 mg/kg/day from infusion of crystalloid IV solutions. This exposure is the same as that cited for TPN administration without added lipid (Attachment 1, pg.11).

The Premasol™ solution covered in the ANDA suitability petition is a crystalline amino acid solution that does not contain lipids. Furthermore, the proposed Premasol™ labeling indicates it is intended for use in a pharmacy admixture program and is restricted to the preparation of admixtures for intravenous infusion. It is not intended for direct infusion and is typically admixed with dextrose, electrolytes and vitamins in a separate container for administration to the patient. The PL 146 Pharmacy Bulk Pack container proposed for Premasol™ in the ANDA suitability petition contains multiple doses and is never used for direct administration to the patient. Furthermore, TrophAmine® is also used in this fashion and therefore, the admixture and use of the proposed Premasol™ solution is no different from that of TrophAmine® when it is removed from its container.

2. B. Braun rejects FDA's estimated exposure for neonates without rebutting FDA's noted foundation and has chosen instead to misinterpret labeling statements from Baxter products other than that proposed for Premasol™ in its ANDA Suitability Petition.

The FDA Safety Assessment estimates an upper bound dose of 0.03 mg/kg/day for neonate (4 kg) DEHP exposure from administration of crystalloid IV solutions and TPN without added lipid. (Attachment 1, pg.11, and supported by Annex A.1.1.1). B. Braun does not provide grounds for challenging this exposure or its basis. However, they do not use this value in their calculations of exposure for a "typical 1-2 kg premature infant" (Braun petition, pg 6). Neither do they challenge statements in FDA's Safety Assessment that the levels of DEHP resulting from the storage of IV crystalline solutions in PVC containers are generally very small in the absence of lipid (Attachment 1, pg.12). Data contained in NDA and ANDA submissions supports the FDA Safety Assessment

with regard to very small to undetectable levels of DEHP in crystalline amino acid solution products packaged in plasticized PVC containers.

The B. Braun petition used a value of 5 ppm for DEHP solutions levels and contended it to be a labeled limit (Braun petition, pg 6). This labeling was not proposed for Premasol™ in the ANDA suitability petition. Neither is reference to the 5 ppm value in other product labeling represented as specific to DEHP or as a limit for it. This value is therefore not appropriate for DEHP exposure calculations. We conclude there is no foundation for using values other than those used by FDA to estimate exposure.

Further, B. Braun has apparently assumed that FDA does not have access to any quantitative information it needs to review DEHP exposure in submitted products. We believe this is presumptive as FDA has the ability to request information it needs to support conclusions of safety.

We conclude based on FDA's DEHP risk assessment and the potential DEHP exposure from the crystalloid Premasol™ product, described in Baxter's ANDA Suitability Petition, that the Premasol™ product poses no risk to infant patient populations due to the potential for DEHP extraction.

Additional discussion addressing some of the specific points made in the B. Braun petition follows. B. Braun's petition points are restated below in bolded text and are followed by our comments.

Comment 1:

“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.” (pg. 2)

“In its Safety Assessment, FDA cites toxic effects of DEHP, and specifically addresses the health risks associated with exposing infants to DEHP.” (pg. 3)

B. Braun has overstated and misconstrued FDA's safety information on DEHP exposure. FDA's Safety Assessment clearly shows that the risks from DEHP exposure in humans are only hypothetical, are based solely on animal studies and that no human data exist to corroborate a definitive risk. FDA's Draft Guidance “Medical Devices Made with Polyvinyl Chloride (PVC) Using the Plasticizer di-(2-Ethylhexyl) phthalate (DEHP)” notes that “although the toxic and carcinogenic effects of DEHP have been demonstrated in laboratory animals, there are no human studies that show such effects”(Attachment 3 – pg 1). In response to the question, “Are children at increased risk of the adverse effects of DEHP, relative to adults?” FDA states: “children undergoing certain medical procedures may represent a population at increased risk for

the effects of DEHP” (Attachment 1 – pg.6.) Infusion of IV crystalloid amino acid solutions is not one of the medical procedures cited by FDA.

Comment 2:

“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.” (pg.2-3)

As noted previously, FDA’s Safety Assessment states “neonates receiving TPN (total parenteral nutrition) with lipid may be at increased risk of DEHP-mediated adverse effects”. However, “in the absence of lipid-containing substances, the amount of DEHP that leaches from PVC storage bags into crystalloid IV solutions is generally very small.” (Attachment 1, pg.12). “There is little to no risk posed by patient exposure to the amount of DEHP released from PVC IV bags following infusion of crystalloid fluids” (Attachment 1, pg.5).

Amino acid solutions for parenteral nutrition are crystalloid IV solutions and are not total parenteral nutrition with lipid. The Premasol™ product described in the ANDA suitability petition is a crystalline amino acid solution that clearly contains no lipids. Furthermore, amino acid solutions delivered to infant populations are not typically administered directly from a DEHP-containing IV container. The clinical standard of practice is to transfer the amino acid solution into a separate container with dextrose, electrolytes and vitamins, which is then used to administer the resulting TPN solution. If lipids are required, they can be added to the separate container or co-infused from a separate container. FDA’s own statements and TrophAmine®’s labeling support these facts. FDA’s Safety Assessment states: “Typical TPN admixtures contain amino acids, dextrose, electrolytes and lipids”(Attachment 1, pg.13). “In addition, non-PVC bags and tubing are typically used to administer TPN, further lessening the concern about DEHP-mediated effects”(Attachment 1, pg 5). TrophAmine’s labeling states “Typically TrophAmine® is admixed with McGaw 50% or 70% Dextrose Injection, USP supplemented with electrolytes and vitamins” (Attachment 4).

It should also be noted that packaging the proposed Premasol™ product in a plastic container offers several advantages over glass. One reason the proposed Premasol™ solution is not packaged in glass is due to potential issues relating to aluminum levels. Additionally, packaging the product in plastic allows the removal of sodium metabisulfite, which may provide a safety benefit for neonates compared to the existing TrophAmine® product, which does contain metabisulfite. Metabolism of metabisulfite requires normal hepatic and renal function to oxidize the bisulfite to sulfite ions for excretion in the urine. Both of these organ systems are immature at birth, particularly in preterm neonates. Sulfite sensitivity may result from the inability to efficiently metabolize metabisulfite. Further, FDA has acknowledged potential safety concerns

associated with metabisulfites in its final rule published in the Federal Register Notice of December 5, 1986. This final rule, "Sulfiting Agents; Labeling in Drugs for Human Use; Warning Statement" requires that a warning statement be included in the labeling of all prescription drugs for human use to which sulfites have been added (see Attachment 5).

Comment 3:

FDA's Public Health Notification provides a list of "highest risk procedures" identified by FDA for DEHP exposure.... 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. (pg.4)

Once again, B. Braun has misstated FDA's publications and the intended use of the Premasol™ product described in the ANDA suitability petition. FDA's Public Health Notification identifies "total parenteral nutrition (TPN) in neonates (with lipids in PVC bag)" as a procedure with high risk of DEHP exposure. (Attachment 2, pg.2). As discussed in Comment 2 above, the intended use of Premasol™ is parenteral nutrition, not total parenteral nutrition with lipids delivered in a PVC container. The proposed Premasol product is a crystalline amino acid solution that clearly contains no lipids.

Comment 4:

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. (pg. 5)

B. Braun quotes FDA's draft guidance titled: "Medical Devices Made with Polyvinyl Chloride (PVC) Using the Plasticizer di-(2-ethylhexyl) phthalate (DEHP)" in making this statement and has misinterpreted its meaning. It is clear from the FDA Safety Assessment upon which the draft guidance is based that FDA's definition of total parenteral nutrition formulae includes amino acids, dextrose, electrolytes and lipids and that the Agency's only concern is with lipid-containing solutions. (see Comment 2 above).

Comment 5:

The B. Braun petition claims FDA rejected “the only” published long-term DEHP study in favor of two unpublished short-term studies by Baxter Corporation (2000) and AdvaMed (2001). (pg. 7)

The B. Braun petition utilizes summary statements from the FDA Safety Assessment regarding potential risk in sensitive patient populations, yet proposes that the calculated tolerable intake (TI) did not consider “...the only long-term study of exposure to DEHP.” (Braun petition at 7). The criticism of the FDA Safety Assessment is without merit because the assessment considered numerous long-term DEHP exposure studies, including special studies in primates (e.g., Kurata, et al., 1998, *Toxicol. Sci.*, 42, 49-56) that were designed to look at the potential for developmental toxicity.

Further, B. Braun asserts that FDA rejected the only long term study (Jacobson et al, 1977) in favor of Baxter and AdvaMed studies “...with 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” (Braun petition at 7). In fact, the Baxter study was a preliminary study that led to the larger, AdvaMed neonatal DEHP study. Both were GLP studies, and the neonatal AdvaMed study was designed and conducted with cooperation and input from the FDA (CDRH) and the U.S. National Toxicology Program’s Center for the Evaluation of Risks to Human Reproduction (CERHR). At the conclusion of these studies, the reports were forwarded to both FDA and CERHR for review and utilization in risk assessment activities. The studies have also been forwarded to the Canadian Health Products Bureau and to the Swedish Ministry of Health. To date, no agency has been critical of the study design, results, or interpretation of the data, and these agencies have utilized the data for risk assessment calculations.

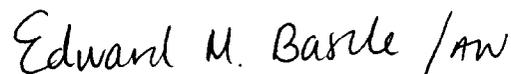
Importantly, the study that was “rejected by the FDA” according to the B. Braun petition, has not been utilized in other regulatory agency assessment activities for sound, scientific reasons. The Jacobson et al (1977) paper *did not even examine the potential for developmental toxicity*; rather it examined the potential for liver toxicity in adult rhesus monkeys. There are a number of technical reasons the study has not been used in quantitative risk assessments, including the fact that the study showed no changes in standard liver function, nor any cancerous or pre-cancerous liver signs. In addition, the number of animals used in the study was so small (only two valid control animals) that statistical analysis was not performed, and the monkey with the highest measured level of DEHP in the liver after transfusion had no liver pathology one year later. Finally, there were several confounding factors in the study that could have affected the results, including the possibility of low-level tuberculosis (there was an outbreak in the monkey colony) and a possible reaction to the foreign protein in the infused blood components from other monkeys.

Conclusion

Based upon these comments, we conclude that the B. Braun petition misrepresents FDA's Safety Assessment and incorrectly alleges a safety concern with crystalline amino acid solutions packaged in DEHP-plasticized PVC containers. In our comments, we have demonstrated that the B. Braun citizen petition has no scientific merit based upon FDA's own Safety Assessment and the intended use and composition of the Premasol™ product described in the ANDA suitability petition. We have illustrated how the B. Braun petition misconstrues and contradicts FDA's published information, takes FDA statements grossly out of context and rejects FDA's own conclusions about the risks of DEHP exposure to neonates. We conclude that there is no scientific or safety concern that supports withholding approval of ANDAs for crystalline amino acid solutions, which are packaged in containers made of DEHP-plasticized PVC and intended for infant patient populations. Therefore, since there is no evidence that the FDA's Safety Assessment is no longer valid, we respectfully request that FDA categorically and expeditiously deny the action requested.

We are also concerned about B. Braun's apparent tactic to misrepresent the safety of crystalloid amino acid solution products in DEHP-plasticized containers and to use the citizen's petition process to delay approval of generic products. We note that although FDA's Safety Assessment has been publicly available for more than one year, B. Braun waited until October 15, 2002 to file the citizen petition allegedly based upon information contained in the FDA Safety Assessment. We respectfully request that FDA dismiss or expedite the review of the B. Braun petition so as not to prolong the approval of a safe generic alternative to the TrophAmine® product.

Sincerely,

Handwritten signature of Edward M. Basile in cursive script.

Edward M. Basile

Enclosures: Attachments 1-5