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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 (Amino Acid Solution Drugs Products Packaged In DEHP-Plasticized PVC For Use In Infants)

Dear Sir/Madam:

We respectfully submit the following comments in further support of our Citizen Petition, which requests that the Food and Drug Administration (FDA) withhold approval of any Abbreviated New Drug Applications (ANDA's) for amino acid solution drug products packaged in polyvinyl chloride (PVC) containers that have been plasticized with di(2-ethylhexyl)phthalate (DEHP) that are intended for use in infant patient populations.

King & Spalding, a law firm, submitted a December 2, 2002 comment in opposition to our Citizen Petition. While the King & Spalding comment does not identify the law firm's client, the only plausible inference is that it is Baxter Healthcare Corporation (Baxter), as the King & Spalding comment consists of a defense of Baxter's proposed ANDA product.

B. Braun stands by its Petition, which is based on FDA's data and articulated concerns. King & Spalding's comments do not address B. Braun's and FDA's concerns with regard to aggregate exposure of infants to DEHP and appears to be an effort to divert attention from Baxter's proposed use of DEHP-plasticized PVC. Rather than presenting their own data to refute FDA's data and concerns, the King & Spalding comment merely relies on unsupported legal argument.

For example, King & Spalding repeatedly states that Baxter's proposed product is a crystalline or crystalloid amino acid solution that does not contain lipids. That statement is correct; indeed, it is true for B. Braun's TrophAmine® (6% and 10% Amino Acid Injections) or any other amino acid solution. However, that statement misses the point, as it is nothing more than an attempt to tie in with FDA's Safety Assessment comments that lipids cause DEHP to leach from an

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intravenous drug container. This does not address our concern: a crystalloid solution (such as Baxter's proposed drug product) alone can cause leaching of DEHP from the container into the drug product. Additionally, it should be noted that lipids are often added to amino acid products (like TrophAmine and Baxter's proposed product) and dextrose to prepare a total parenteral nutrition (TPN) solution to provide "complete nutrition in one container" for patients. These lipid-containing admixtures are never put into a TPN bag containing DEHP. This fact is well known by pharmacists and is not relevant to our argument, although King & Spalding chooses to focus on it as part of their effort to cloud the real issue.

Below are calculations of the amount of DEHP that could be present in a dose of an amino acid solution administered to a neonatal intensive care unit (NICU) patient:

a) Based on the TrophAmine® dosage recommendations (2.0 – 2.5 grams (g) of amino acids/kg/day), a neonate weighing 2 kg would receive a PremaSol ™ dose of up to 50 mL/day. According to Baxter's Package Insert for Dextrose Injection, USP, as much as 5 ppm (0.005 mg/mL) of DEHP can leak from the container into the solution. (Attachment 1, pg.1) If this labeled amount is used for the maximum neonatal exposure calculation, a 50 mL PremaSol dose would contain 0.125 mg/kg/day of DEHP. This dose of DEHP is about 21% of the IV tolerable intake (TI) of 0.6 mg/kg/day (Attachment 2, pg. 4).

b) In a recently published review article by Dennis Jenke (of Baxter Healthcare), DEHP levels in crystalloid solutions were reported to be as high as 3900 µg/L. (0.0039 mg/mL) (Attachment 3, pg. 338) In this case, a 50 mL dose of crystalloid solution such as PremaSol could contain 0.195 mg of DEHP, which equates to approximately 33% of the IV TI. Clearly, doses of this magnitude, when taken in aggregate with other sources of DEHP to which NICU patients are exposed for weeks or even months on end, should be of serious concern to patients and their healthcare providers. King and Spalding's comments failed to address the aggregate exposure to DEHP for neonates.

In its Safety Assessment the FDA emphasized that "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." In a NICU setting, a neonate often undergoes multiple procedures involving medical products plasticized with DEHP. In the Safety

Assessment the FDA further states, "Based on the dose of DEHP received in such procedures as intravenous administration of sedatives, administration of TPN and replacement transfusions, all common procedures in the NICU, it is possible to estimate that a 4 kg infant [note: more common weight for premature neonate is 1-2 kg] could receive a DEHP dose on the order of 3 mg/kg/day for a period 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" (Attachment 2, pg. 6). This does not take into account the amount of DEHP that could leach from IV solutions.

King and Spalding's contention that PremaSol, an amino acid crystalloid solution, does not leach DEHP is false.

Numerous studies demonstrate that DEHP leachability in crystalloid solutions is significant enough to raise concerns over neonatal exposure to DEHP-containing PVC crystalloid solutions.[1,2] As noted in item b above, 33% of the IV TI can be delivered in 50 ml of a crystalloid solution. This cannot be considered an insignificant amount, especially when applied to NICU patients who undergo numerous medical procedures, many of which expose them to even higher levels of DEHP than those delivered during IV ministration of a crystalloid solution. Given the absence of a pediatric TI, the uncertainty associated with the toxic effects of long-term exposure to DEHP, and the FDA's concern over aggregate exposure of critically ill neonates to DEHP, the 33% of the TI level raises concern over the safety of DEHP in crystalloid solutions packaged in DEHP-plasticized IV containers. Furthermore, factors like temperature, agitation and timing promote DEHP leaching.[3] Therefore, the amount of DEHP that could be infused into a neonate may actually be higher than 33% of the IV TI.

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[1] Safety Assessment of Di (2-ethylhexyl) phthalate (DEHP) Released from PVC Medical Devices. Center for Devices and Radiological Health, Food and Drug Administration, July 2002.

[2] NTP – CERHR Expert Panel Report on Di (2-ethylhexyl) phthalate. National Toxicology Program, U.S. Department of Health and Human Services, Center for the Evaluation of Risks to Human Reproduction, October 2000.

[3] Rustamova I: To use or not to use plasticized PVC bags. University of California at San Francisco Drug Product Services Laboratory, January 2000.

King & Spalding's allegation that the study by Jacobson et al. (1977) "has not been utilized in other regulatory agency assessments for sound, scientific reasons" is without merit. We have attached the comments received from Drs. Jacobson and Kevy, which respond to the points made by the Agency in the Safety Assessment (Attachment 4, pg. 3). We believe that these comments adequately address King & Spalding's concerns.

King & Spalding's statements on page 4 of their letter regarding the potential for migration of aluminum from glass packaging and reference to the presence of sulfites in TrophAmine have nothing to do with the subject of our Petition. TrophAmine has been approved as safe and effective and complies with all applicable FDA regulations.

Our concerns with Baxter's proposed use of DEHP-plasticized PVC containers for its proposed generic version of TrophAmine are supported by our December 5, 2002 comment to FDA Docket No. 02D-0325, regarding the Draft Guidance on Medical Devices Made With Polyvinylchloride (PVC) Using the Plasticizer di-(2-Ethylhexyl)phthalate (DEHP) (Attachment 4).

Conclusion

For the reasons discussed, it is our view that the King & Spalding comments do not raise any significant issues and do not counter the relief sought in our Petition. Thus, B. Braun urges the Agency to grant the relief sought in our Citizen Petition without delay.

B. Braun appreciates the Agency's attention to this important matter.

Respectfully submitted,

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