



## **A.S.P.E.N. Intravenous Trace Element Shortage Survey Report**

**June 2014**

A.S.P.E.N. Clinical Practice Committee and Nutrition Product Shortage Subcommittee

### **Introduction**

The shortage of parenteral nutrition (PN) components has been ongoing since 2009. The shortage of intravenous (IV) trace elements as adult, pediatric and neonatal multi-trace element products and individual trace element entities has been particularly concerning as administering PN with less than optimal amounts of trace elements has been associated with deficiencies and patient harm.<sup>1-7</sup> There were only two FDA-approved U.S. manufacturers (American Regent and Hospira, Inc.) of these trace element products and release of products has been hindered and sporadic due to manufacturing delays.<sup>8-9</sup> Due to these shortages, the FDA approved importation of multi-trace and single element products in order to fill the patient need and gaps in the market.<sup>10-11</sup> The A.S.P.E.N. Clinical Practice Committee Nutrition Product Shortage Subcommittee was interested in learning more about how clinicians are managing the prolonged shortage IV trace elements and evaluating the impact of these shortages on their patients.

### **Methods**

The Shortage Subcommittee developed a survey to provide clinicians the opportunity to share their current clinical experiences and shortage management practices. The survey was composed of 71 questions and was made available online using SurveyMonkey® (Palo Alto, CA). The survey was announced in the March 25, 2014 *Insight Weekly*, A.S.P.E.N.'s electronic newsletter

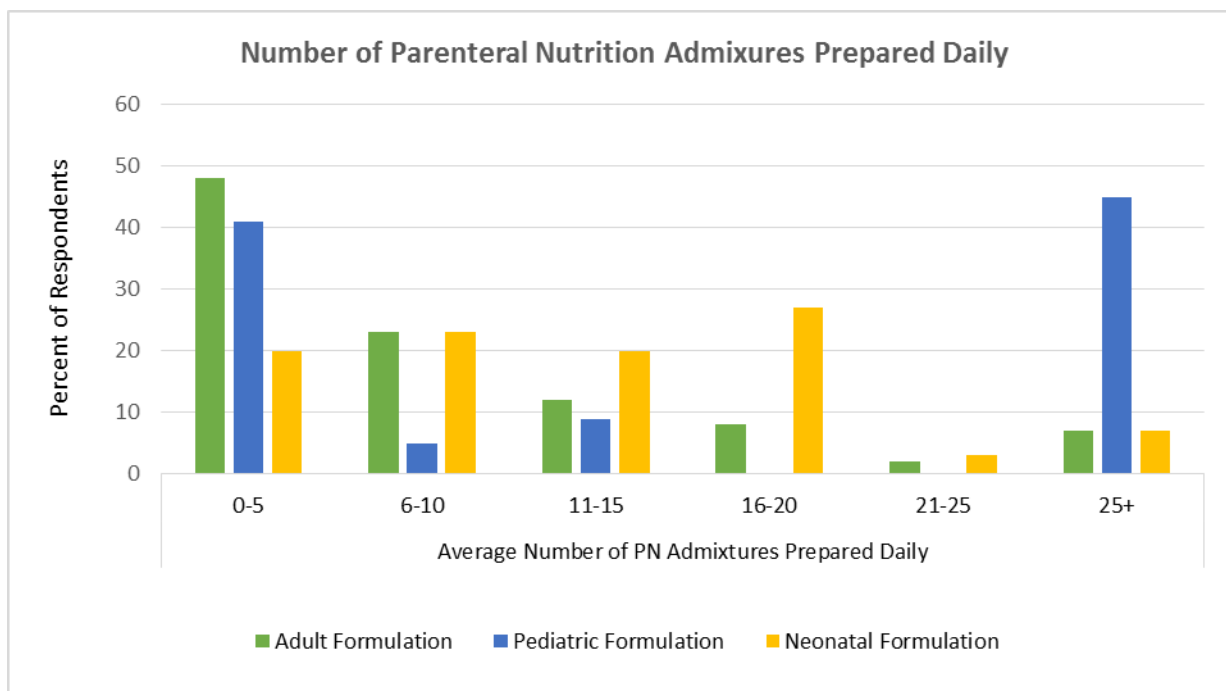
and the March 27, 2014 Institute for Safe Medication Practices *Medication Safety Alert!* The announcement included a link for participants to voluntarily access the questionnaire. The survey was available to participants for 4 weeks (March 25-April 21, 2014).

## Demographics

A total of 297 responses were received. The respondents self-identified as pharmacists (54%), dietitians (30%), physicians (7%), nurses (3%), and others (6%). Of the pharmacists responding, 82% identified their primary practice site as hospital pharmacy and 15% reported home infusion. For all other respondents, 74% work in an acute care hospital and 14% in home care.

Most respondents (86%) provide PN therapy to adult patients. Thirty-eight percent of respondents provide PN to pediatric patients and 39% to neonates; respondents were able to check all that apply for those who care for more than one population. For respondents preparing PN admixtures for adult patients, almost half (47%) reported the average number of PN prepared is 0-5 per day. In contrast, 45% of those preparing PN admixtures for pediatric patients reported they prepare >25 PN admixtures per day. (See Figure 1.)

Figure 1. Number of Parenteral Nutrition Admixtures Prepared Daily



## Results

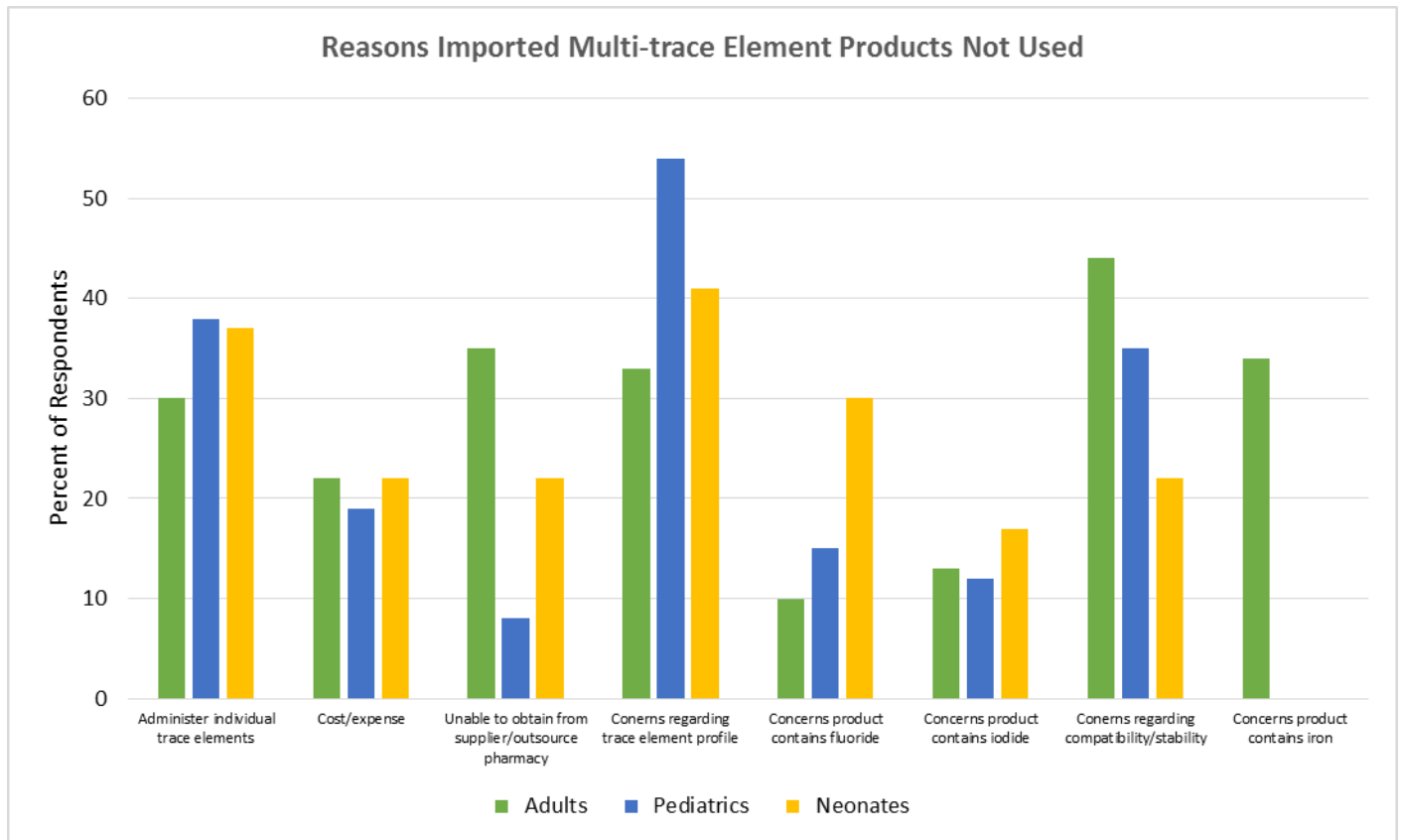
### *Adults*

When asked about the availability of U.S. commercially available IV adult multi-trace element product, 40% of respondents indicated the product is available in their healthcare organization. However, only 43% administer a full dose daily. All others reported using a conservation and/or rationing strategy such as administering a full dose 3 times a week or a half dose daily.

Respondents that did not have U.S. commercially available IV adult multi-trace element product were queried about the availability of the imported European product in their organization and if used, the current dosing regimens. About half of respondents reported availability of the imported European IV adult multi-trace element product and of these, 42% administer a full dose daily, and 58% have dosing regimens ranging from one-third to one-half dose daily to a full dose 3 times per week. Although the product literature for the imported European product cautions against adding the product to PN admixtures containing IV fat emulsion due to the risk of disrupting the emulsion, almost one-third (28%) of respondents reported adding the product to a total nutrient admixture (TNA) PN and none reported any incompatibilities or unstable admixtures. Fifty-eight percent of those using the imported European product add it to dextrose-amino acids PN admixtures with the remaining respondents adding it to either a small or large volume IV fluid.

Those respondents that did not have the U.S. commercially available IV adult multi-trace element product available and were not using the imported European product provided reasons for not using the imported product. The most common reasons are illustrated in Figure 2. The respondents were asked to check all that apply.

Figure 2. Reasons Imported Multi-trace Element Products Not Used



Almost half (53%) of respondents providing PN to adult patients reported individual trace elements are added to PN admixtures. Zinc is most commonly administered followed by selenium, copper and manganese. When asked about the source of individual trace elements, 14% reported they administer compounded products made in-house as well as obtained from external compounding pharmacies. Only 2% of respondents reported administering the imported European zinc gluconate trihydrate. The primary reason for not using this product was the availability of a U.S. commercially available zinc injection.

Although administering neonatal and pediatric multi-trace element products to adults is discouraged, 11% of the respondents providing PN to adults reported they administer the neonatal product to adults and 9% reported the pediatric product is administered to adults receiving PN.

About half of the respondents providing PN to adults indicated they monitor for trace element deficiencies assessing clinical signs and symptoms, laboratory parameters or both.

### *Pediatrics*

The U.S. commercially available IV pediatric multi-trace element product is available to 40% of the respondents who reported providing PN to pediatric patients. Most (82%) administer a full dose daily to pediatric patients receiving PN. The remaining provide a reduced dose of multi-trace elements.

Those respondents that reported not having the U.S. commercially available pediatric multi-trace element product were asked about the use of the imported European IV pediatric multi-trace element products. Only 38% indicated the product is used in their healthcare organizations. Although this product is available, 30% of respondents reported using a dosing regimen giving less than a full dose daily (e.g., full dose 3 times per week, 50% dose daily). Of the respondents using the imported European multi-trace element product, 45% reported they add the product to a TNA PN admixture. As with those adding the adult imported product to TNA PN, none reported any unstable or incompatible admixtures. All others using the imported pediatric multi-trace element product administer it in dextrose-amino acids PN admixtures.

Those respondents not using the imported IV pediatric multi-trace element product were asked to indicate the reason(s) the product is not used. The most common reasons are noted in Figure 2.

Two-thirds of respondents providing PN to pediatric patients reported they administer individual trace element entities. Almost all (97%) provide zinc, followed by selenium (68%), copper (65%) and manganese (41%). About 80% of those administering individual entities obtain U.S. commercially available products. The remaining administer compounded products prepared in-house or procured from an external compounding pharmacy. Similar to those providing PN to adults, the imported European zinc gluconate trihydrate was used by less than 5% of respondents providing PN to pediatric patients.

Administering the U.S. IV adult multi-trace element to pediatric patients was reported by 20% of respondents. Another 20% also reported administering the neonatal multi-trace element product to pediatric patients receiving PN. Sixty-one percent of respondents providing PN to pediatric patients indicated they monitor for trace element deficiencies by clinical signs and symptoms, laboratory parameters or both.

### *Neonates*

Clinicians providing PN to neonates were queried on the availability of the U.S. commercially-available IV neonatal multi-trace element product. Only 30% reported this product is available in their healthcare organization. For those having the neonatal product, 31% administer less than the recommended daily dose, that is, most do not employ a rationing/conservation dosing regimen.

Of those neonatal clinicians that do not have the U.S. IV neonatal multi-trace element product, only one-third reported administering the imported European IV pediatric multi-trace element product to neonates. When the imported product is used, most (91%) administer the daily recommended dose. Of those not using the imported pediatric product, 37% reported administering individual trace element entities. Other frequently reported reasons for not using the imported pediatric product are noted in Figure 2. Similar to those caring for pediatric patients, about two-thirds reported administering compounded individual trace element entities. Almost all that administer compounded products provide zinc, about two-thirds give selenium and copper, and one-quarter give manganese. Sixty-seven percent of compounded trace elements provided to neonates are procured from outsourced pharmacies. The imported European zinc gluconate trihydrate injection is not used in this patient population due to the availability of a U.S. commercially available IV zinc product.

Almost one-third of respondents providing PN to neonates reported administering the U.S. IV pediatric multi-trace element product to neonates. A small number of respondents (6%) reported giving the U.S. adult product to neonates.

Almost half of the respondents that provide PN to neonates reported that they monitor for trace element deficiencies. Similar to those caring for pediatric patients receiving PN, three-quarters assess both clinical signs and symptoms and laboratory parameters to identify trace element deficiencies.

#### *Adverse Events and Suboptimal Patient Outcomes*

Clinicians responding to the survey were offered the opportunity to describe any adverse events or suboptimal patient outcomes (without patient identifiers) associated with the shortages of IV trace elements. Forty one percent of respondents reported suboptimal patient outcomes associated with the shortages and 27% specifically stated deficiencies of zinc, copper and selenium. In contrast, almost half (45%) of respondents specifically indicated that they had not observed any adverse events or suboptimal patient outcomes associated with the shortage of trace elements.

#### **Discussion**

The results of this survey of clinicians providing PN to adult, pediatric and neonatal patients provides insight into the practices and strategies for managing the prolonged shortage of IV trace elements. Less than half of these respondents have the U.S. commercially available, population-specific, IV multi-trace element products. When these products are available and prescribed, rationing and conservation dosing regimens are common, even for neonates, a population that is most vulnerable for developing deficiencies. Furthermore, clinicians are administering U.S. commercially available products to patient populations other than those for whom they are intended. This practice may contribute to product shortages as well as to the risk of trace element under dosing or over dosing.

Since May 2013, imported European IV adult and pediatric multi-trace element products have been available in the U.S. Despite the availability of these imported European products in the U.S., they are not widely used by clinicians who are unable to obtain U.S. products. Even when the imported European product is available to clinicians, not all administer a full dose daily in PN

admixtures, even to pediatric and neonatal patients who are the greatest risk of developing deficiencies.

About one-third of respondents indicated they do not use the imported European IV multi-trace element products because individual trace element entities are available. For others, the most common reasons for not administering the imported European IV multi-trace element products are concerns about the trace element profile and concerns about compatibility/stability with PN admixtures. Although the elements and the doses in the European multi-component products are different than those of the U.S. commercially-available products, the products are used extensively in Europe. Furthermore, the adequacy of the current U.S. IV adult, pediatric and neonatal multi-trace element profiles has been questioned and recommendations made to modify the profiles.<sup>12</sup> The compatibility and stability concerns for adding the imported European IV adult multi-trace element product PN admixtures, especially those containing IV fat emulsion may be warranted. This product contains iron (ferric chloride), which when mixed with IV fat emulsion may result in an unstable PN admixture. However, the FDA-approved Dear Healthcare Professional Letter for the product describes adding the product to dextrose-amino acids PN formulations thereby avoiding the risk of an unstable PN.<sup>13</sup> This recommended method of administration can be used to safely deliver the imported IV multi-trace element products and was the method reported by most respondents who give this product. As for the imported IV pediatric multi-trace element product, the information in the Dear Healthcare Professional Letter states the product is physically compatible with the electrolytes and vitamins usually present in the dextrose-amino acids PN admixtures.<sup>14</sup> With careful planning and adjustment in administration methods, PN admixtures containing these imported IV multi-trace element products can be administered to patients.

Other reported reasons for not using imported products include unable to obtain from supplier/wholesaler or outsource compounding pharmacy and concerns about the expense. Clinicians who are unable to procure these products should be persistent in discussions with purchasers and suppliers including requesting the products by proprietary name and/or NDC code or



directly contacting the U.S. distributor/manufacturer. The additional expense should not be an acceptable reason for a patient on PN to become nutrient deficient.

Approximately half of all clinicians responding to the survey indicated they monitor for trace element deficiencies by assessing clinical signs and symptoms and/or laboratory parameters. Yet 45% of respondents stated they had not observed any adverse events or suboptimal patient outcomes associated with the trace element shortages. Significant number of respondents do not administer full doses of multi-trace element products and prolonged less than optimal dosing of trace elements may result in deficiencies. Clinicians may not readily identify deficiencies as clinical signs and symptoms are non-specific and laboratory parameters may lack sensitivity for assessing deficiencies.

### **Conclusion**

The shortage of U.S. commercially available IV trace elements has been ongoing for over 5 years. During this time clinicians have implemented rationing and conservation strategies to extend the limited supply of products in order to provide some amount of trace elements to patients.<sup>15-20</sup> As an effort to relieve the critical shortage, the FDA approved the temporary importation of IV multi-trace element and single entity products. Even though U.S. commercially available trace elements (although limited supply) and imported trace elements are available, patients continue to receive PN with inadequate dosing of trace elements. Although there have been reports of deficiencies in the scientific literature, many of the respondents to this survey did not report any adverse events or suboptimal patient outcomes even when monitoring for deficiencies. The lack of observed adverse events/deficiencies and the potential cost savings associated with “partial” dosing of trace elements should not be the impetus to continue this practice of less than optimal dosing of trace elements. Now is the time to evaluate current practices for dosing IV trace elements, review IV trace element requirements for patients receiving PN and implement daily dosing regimens to meet the trace element needs for all patients receiving PN every day.

### **Take Away Messages**

- Prescribe and administer full required dose of trace elements daily in patients who require it.
- Use the population-specific product only for the appropriate population.
- Consider use of imported products when U.S. products are not available.
- Use the imported products according to the Dear Healthcare Letter instructions.
- Be persistent in trying to obtain products from the manufacturer or distributor.
- Monitor patients closely where they are receiving lower than required doses.

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