Small Volume Parenteral Drug Products and Pharmacy Bulk Packages for Parenteral Nutrition: Aluminum Content and Labeling Recommendations

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Clinical/Medical
Revision 1

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Small Volume Parenteral Drug Products and Pharmacy Bulk Packages for Parenteral Nutrition: Aluminum Content and Labeling Recommendations
Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

Aluminum toxicity from prolonged use of parenteral nutrition (PN) represents a major safety concern, particularly in patients with renal impairment or pediatric patients with immature renal function. This guidance is intended to assist sponsors and applicants of small volume parenteral (SVP) drug products[2] and pharmacy bulk packages (PBPs)[3] in meeting the requirements in 21 CFR 201.323 to control aluminum contamination in PN drug products. Although 21 CFR 201.323 uses the term "total parenteral nutrition" (TPN), meaning PN providing 100 percent of a patient's nutritional needs, the same PN products are used whether providing all of a patient's nutritional needs or only a portion of their nutritional needs. This guidance clarifies the key factors in calculating the aluminum content to ensure that the total aluminum exposure (TAE) from PN does not exceed an acceptable threshold.[4] It also provides FDA's recommendations regarding the aluminum concentration limits (ACLs) for SVPs. The recommendations for TAE and ACL in this guidance apply to SVPs that are the subject of new drug applications (NDAs), abbreviated new drug applications (ANDAs), and supplements to those applications.

[1] This guidance has been prepared by the Division of Hepatology and Nutrition in collaboration with the Labeling Policy Team within the Office of New Drugs, the Office of Pharmaceutical Quality, and the Office of Generic Drugs in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] For the purposes of this guidance we use the terms *SVP drug product* and *SVP* interchangeably; *SVPs* refer to products packaged as single doses in a container with a capacity of less than 100 milliliters or SVPs packaged as PBPs for use in PN.

[3] PBPs are sterile preparations for dispensing of single doses to many patients in a pharmacy admixture program. PBPs are used to prepare admixtures for infusion or to fill empty sterile syringes (through a sterile transfer device). PBPs are limited to *injection*, *for injection*, or *injectable emulsion* dosage forms. See United States Pharmacopeia (USP) General Chapters <7> Labeling and <659> Packaging and Storage Requirements.

[4] The recommendations in this guidance do not apply to the aluminum adjuvants used in vaccines to elicit a stronger immune response.

Aluminum content of large volume parenteral (LVP) drug products[5] must not exceed 25 micrograms per liter (mcg/L).[6] However, the limits for the aluminum content of SVPs are not specified by statute or regulation. Further, the International Council for Harmonisation (ICH) has not established a permitted daily exposure (PDE) for aluminum.[7]

Due to the potential health risks from long-term exposure to aluminum, as explained in the Background section below, FDA aims to have sponsors and applicants limit the individual aluminum exposure (IAE) in each drug product to ensure that the TAE from all components of PN in an admixture (LVPs plus SVPs) does not exceed 4 to 5 micrograms/kilogram/day (mcg/kg/day) of aluminum, a level above which toxicity may occur (as described in 21 CFR 201.323(e)). To achieve these aims, FDA recommends sponsors and applicants develop mitigation and control strategies to reduce aluminum contamination in their drug products through formulation design optimization, raw material and component control, manufacturing equipment and process optimization, and selection of appropriate container and closure system(s).

This guidance does not alter concentration limits for aluminum content in LVPs because those are addressed in 21 CFR 201.323. However, LVPs and SVPs are often used together in PN; therefore, this guidance considers the aluminum content in LVPs when calculating the recommended ACL in an SVP.

Additionally, this guidance is intended to assist sponsors and applicants in determining the appropriate placement of information on aluminum toxicity in SVP and LVP Prescribing Information and container and carton labeling.[8] In particular, this guidance aims to ensure that this information in labeling is clear to health care practitioners and guides the safe and effective use of the drug product.

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[5] For the purposes of this guidance, a *large volume parenteral drug product* has the same meaning as in 21 CFR 310.509(b): a terminally sterilized aqueous drug product packaged in a single-dose container with a capacity of 100 milliliters or more and intended to be administered or used intravenously for PN in a human. For the purposes of this guidance we use the terms *LVP drug product* and *LVP* interchangeably.

[6] 21 CFR 201.323(a).

[7] PDE is defined as the maximum acceptable intake of elemental impurity in pharmaceutical products per day. See the ICH guidance for industry *Q3D(R2) Elemental Impurities* (September 2022) (ICH Q3D(R2)). The ICH guidance does not provide a PDE for aluminum because of differences in regulations and practices among geographic regions.

[8] See 21 CFR 201.56(d) and 21 CFR 201.57. See also 21 CFR 201.323. The labeling examples in this guidance are for prescription SVPs and PBPs with labeling that meets the requirements of 21 CFR 201.56(d) and 21 CFR 201.57 (physician labeling rule (PLR) format). FDA recommends that the applicant discuss incorporating aluminum toxicity information in SVP labeling that meets the requirements of 21 CFR 201.56(e) and CFR 201.80 with the FDA prescription drug review division. FDA encourages holders of new drug applications whose labeling are not required to have labeling in PLR format to voluntarily convert their labeling to PLR format because the PLR format represents a more useful and modern approach for communicating information on the safe and effective use of drug products, and it makes Prescribing Information more accessible for use with electronic prescribing tools and other electronic information resources.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Parenteral drug products are those intended for injection through the skin or other external boundary tissue, rather than through the alimentary canal, so that the drug products' active substances are administered directly into a blood vessel, organ, tissue, or lesion. PN is a source of calories, protein, electrolytes and essential fatty acids in patients for whom oral or enteral nutrition is not possible, is insufficient, or is contraindicated. SVPs may be components of PN admixtures.

Aluminum, one of the most abundant metallic elements on earth, occurs naturally in several minerals, ores, oxides, and silicates. Humans are exposed to aluminum through drinking water, foods, and drugs. Aluminum's oral bioavailability is poor, so healthy individuals typically face little risk of toxicity. The gastrointestinal tract allows less than one percent of ingested aluminum to be absorbed into the bloodstream, and renal excretion removes 99 percent of that aluminum. However, in the settings of chronic kidney failure[9] or prolonged PN treatment in neonates,[10,11] aluminum toxicity has manifested as osteomalacia and reduced bone mineralization, neurological dysfunction including dialysis encephalopathy, microcytic hypochromic anemia, and cholestasis.

PN ingredients may be contaminated with aluminum from raw materials as well as from byproducts generated during the manufacturing and packaging process, where aluminum may leach from the manufacturing equipment and/or container closure components (e.g., glass vials, stoppers) during autoclave terminal sterilization and shelf-life storage. Therefore, PN can be a source of aluminum exposure. Patients with underlying renal impairment who receive prolonged courses of PN are at greatest risk of exposure to toxic levels of aluminum from PN. Preterm neonates and infants,[12] who have immature kidneys that are incapable of excreting aluminum efficiently and who may require weeks of PN before transitioning to oral nutrition, are at particularly high risk.

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[9] See, for example, Boyce BF, GS Fell, HY Elder, BJ Junor, HL Elliot, G Beastall, I Fogelman, and IT Boyle, 1982, Hypercalcaemic Osteomalacia Due to Aluminium Toxicity, Lancet, 2(8306):1009–1013, doi: 10.1016/s0140-6736(82)90049-6. PMID: 6127501.

[10] Bishop NJ, RM Morley, JP Day, and A Lucas, 1997, Aluminum Neurotoxicity in Preterm Infants Receiving Intravenous-Feeding Solutions, N Engl J Med, 336(22):1557–1561.

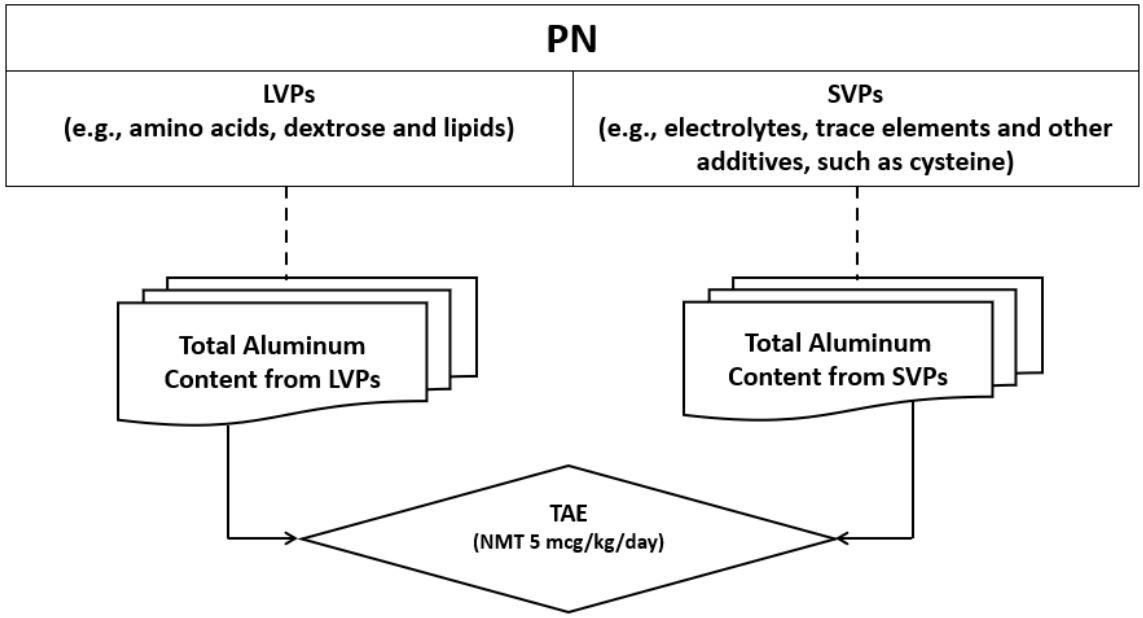
[11] Fewtrell MS, NJ Bishop, CJ Edmonds, EB Isaacs, and A Lucas, 2009, Aluminum Exposure From Parenteral Nutrition in Preterm Infants: Bone Health At 15-Year Follow-Up, Pediatrics, 124(5):1372–1379.

[12] The term *neonate* includes the age range from birth to up to 1 month of age, and the term *infant* includes the age range from 1 month to up to 2 years of age. The terms *preterm infant* and *premature infant* include birth before 37 weeks of gestation.

In one controlled trial,[10] preterm neonates were randomized to receive PN with standard aluminum content (mean of 45 mcg/kg/day) or aluminum-depleted PN (mean of 4 to 5 mcg/kg/day). Patients treated with standard PN for more than 10 days had lower scores on developmental assessments at 18 months compared with the aluminum-depleted PN group. A follow-up study that evaluated a subset of survivors at age 13 to 15 years showed lower bone mineral content in the lower lumbar spine and hips in the group treated with standard PN.[11] Accordingly, FDA recommends that the TAE from PN should not exceed 4 to 5 mcg/kg/day to protect the safety of all patients.

Multiple sources of LVPs and SVPs comprise PN, and each drug product contributes to the total aluminum content of PN. Sponsors and applicants should consider the recommended aluminum limit in an individual SVP because the aluminum limit determines the drug product's contribution to the total daily aluminum exposure from PN. The individual SVP aluminum limit is needed to support the calculations for determining whether addition of the SVP will cause the TAE to exceed 5 mcg/kg/day (see Figure 1).

Figure 1. Schematic of Aluminum Contributions in PN



PN = parenteral nutrition, LVP = large volume parenteral, SVP = small volume parenteral, TAE = total aluminum exposure, NMT = no more than; mcg = microgram; kg = kilogram.

III. STEPS TO DERIVE THE RECOMMENDED ACL IN THE SVP

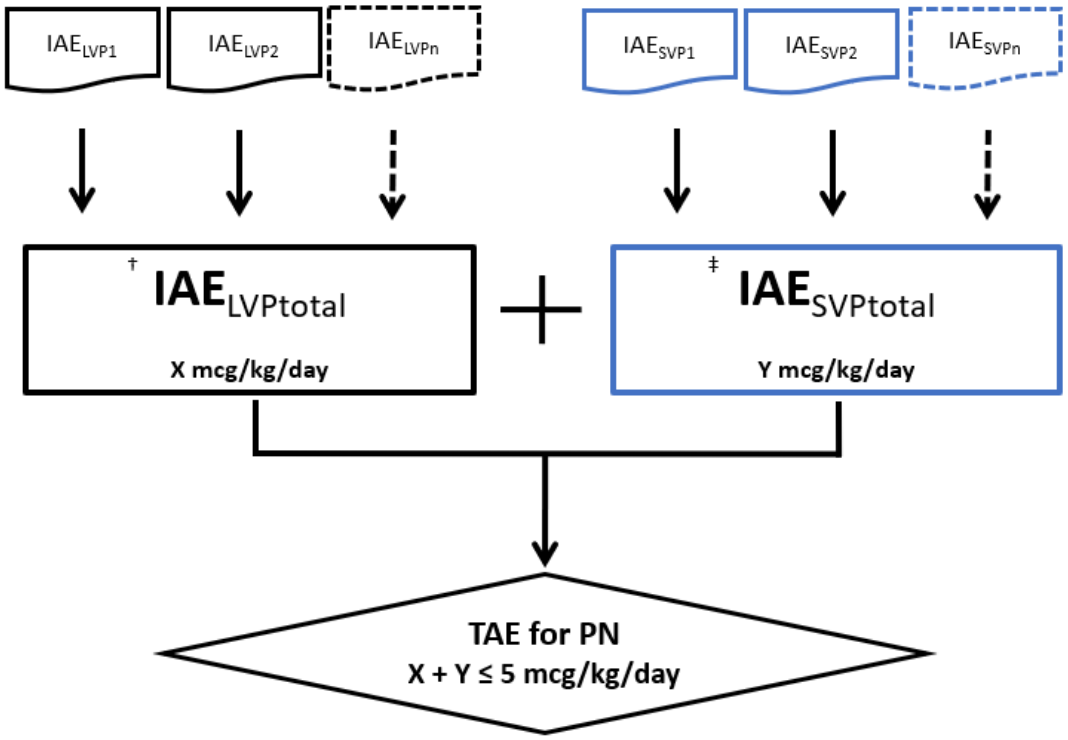
There are two major steps in deriving the ACL in an SVP. First, the sponsor or applicant selects the IAE expressed as mcg/kg/day of the individual SVP (see section IV.A., Calculation of IAE_{SVP} Based on the Known or Labeled Aluminum Concentration for an Approved SVP); then the sponsor or applicant can use the IAE to calculate the ACL for each specific SVP (see section IV.B., Calculation of the ACL Based on a Selected IAE_{SVP} for SVPs Under Development).

A. Selection of the IAE of Individual SVP

The first step in calculating the ACL for the specific SVP is the selection of the IAE. The IAE should be selected to ensure that the addition of the SVP to a PN admixture containing multiple SVPs and LVPs will not cause the TAE to exceed 5 mcg/kg/day. The number of SVP additives will vary for individual patients based on their nutritional needs. A practical approach for ensuring that the addition of SVPs to PN admixtures does not result in TAE values greater than 5 mcg/kg/day is to select a single (constant) IAE. Selection and application of the IAE should occur during the early developmental stages of SVPs.

Figure 2 provides a conceptual overview of the aluminum exposure contributed by the multiple LVPs and SVPs that comprise PN as a basis for the Agency's recommended approach for selecting an IAE for SVPs (described after Figure 2).

Figure 2. Contribution of IAE to TAE for PN



IAE = individual aluminum exposure; TAE = total aluminum exposure; PN = parenteral nutrition; LVP = large volume parenteral; SVP = small volume parenteral; IAE_{LVP} = individual aluminum exposure from LVP drug product; $IAE_{LVPtotal}$ = total aluminum exposure from LVPs; IAE_{SVP} = individual aluminum exposure from SVP; $IAE_{SVPtotal}$ = total aluminum exposure from SVPs.

† $IAE_{LVPtotal}$ = 0.025 micrograms/milliliters (mcg/mL) times (mL of LVPs/kilograms (kg)/day). Actual measured aluminum concentration in the LVP may be lower than 25 mcg/liter (L), but the aluminum concentration in the LVP is assumed as 25 mcg/L per 21 CFR 201.323.

‡ $IAE_{SVPtotal}$ = Y mcg/kg/day divided by the number of SVPs intended for use in PN.

For this approach, the recommended IAE for an individual SVP is 0.6 mcg/kg/day or lower. Selection of 0.6 mcg/kg/day as the constant IAE_{SVP} allows for the addition of up to five SVPs with reasonable assurance that the TAE will not exceed 5 mcg/kg/day, based on the expectation that the total aluminum exposure from LVPs ($IAE_{LVPtotal}$) will not exceed 2 mcg/kg/day (aluminum is controlled at 25 mcg/L in LVPs, per 21 CFR 201.323). Further, if use of more than five SVPs in a PN admixture is anticipated, then the selection of an IAE_{SVP} should be substantially lower than 0.6 mcg/kg/day to ensure that the TAE will not exceed 5 mcg/kg/day.

1. TAE from LVP (X mcg/kg/day or $IAE_{LVPtotal}$)

a. The IAE for each LVP (in mcg/kg/day) is calculated from the daily dose volume (milliliter/kilogram/day (mL/kg/day)) of the LVP and its aluminum concentration (mcg/L).

b. The aluminum concentration in each LVP component used in a PN admixture must not exceed 25 mcg/L.[13] Therefore, this guidance assumes a maximum aluminum concentration of 25 mcg/L (or 0.025 mcg/mL) to determine each $IAE_{LVPtotal}$.

Example: For a 3 kg infant receiving a daily dose volume of 80 mL/kg/day of LVP_{1+2+n}, the maximum aluminum contribution from LVPs (X mcg/kg/day or $IAE_{LVPtotal}$) would be 2 mcg/kg/day (i.e., 0.025 mcg/mL times 80 mL/kg/day). The infant would be exposed to a maximum of 6 mcg/day (i.e., $IAE_{LVPtotal}$ times 3 kg) of aluminum from the LVP.

2. TAE from SVP (Y mcg/kg/day or $IAE_{SVPtotal}$)

a. TAE from SVPs can be calculated by subtracting the $IAE_{LVPtotal}$ aluminum contribution from the TAE for the total amount of PN (e.g., 5 mcg/kg/day) or Y mcg/kg/day equals 5 mcg/kg/day minus X mcg/kg/day.

Example: If TAE from the LVP ($IAE_{LVPtotal}$) is X equals 2 mcg/kg/day, given that the TAE for the total amount of PN is 5 mcg/kg/day, Y should be no more than 3 mcg/kg/day ($IAE_{SVPtotal}$).

b. SVPs can be used alone or in combination with other SVPs as additives (i.e., electrolytes, trace elements, vitamins, amino acids), which will all contribute toward the $IAE_{SVPtotal}$.

As described above in section III.A., the IAE from an individual SVP (IAE_{SVP}) should be selected as 0.6 mcg/kg/day or lower. This approach takes into consideration the number of SVPs intended to be used in the PN admixture and the known IAE_{SVP} of each individual SVP. A typical PN admixture can include approximately four to six SVP additives, but this can vary depending on the specific SVP indication and an individual's nutritional needs.

Selection of 0.6 mcg/kg/day as the default IAE_{SVP} allows for the addition of up to five total SVPs in PN admixtures with reasonable assurance that the TAE will not exceed 5 mcg/kg/day. Selection of an IAE_{SVP} less than 0.6 mcg/kg/day may enable the use of more than five SVPs in PN admixtures, with a similar assurance that the TAE will not exceed 5 mcg/kg/day.

B. Calculation of the ACL in an SVP

The selected IAE for an SVP should be used to calculate the ACL in mcg/L as shown in the formula below.

[13] See 21 CFR 201.323(a).

$$\text{SVP ACL (mcg/L)} = 1000\,\frac{\text{mL}}{\text{L}} \times \left(\frac{\text{IAE (mcg/kg/day)} \times \text{SVP concentration (mg/mL)}^{14}}{\text{SVP max. daily dosage (mg/kg/day)}}\right)$$

The acceptance criteria of the aluminum concentration in the SVP specification should not exceed the ACL. This will ensure that the total aluminum the patients receive from PN will not exceed 5 mcg/kg/day.

IV. EXAMPLES OF CALCULATION OF IAE AND ACL

This section provides examples of the calculation of IAE_{SVP} from SVPs with known aluminum concentrations (part A) and calculations of ACL for hypothetical examples of SVPs under development based on the recommended dosages and drug (nutrient) concentrations (part B).

A. Calculation of IAE_{SVP} Based on the Known or Labeled Aluminum Concentration for an Approved SVP

When there is an SVP with a known or labeled aluminum concentration (Al concentration in formulas) (e.g., zinc chloride, multivitamins, cysteine hydrochloride), the projected aluminum exposure from the SVP (mcg/kg/day) or IAE_{SVP} of an individual drug product can be calculated using the following formula when the specific SVP maximum dose is expressed in mg/kg/day:

$$\text{IAE (mcg/kg/day)} = \frac{\text{Al concentration } \left(\frac{\text{mcg}}{\text{L}}\right) \times \text{SVP max. daily dosage (mg/kg/day)}}{1000\ \frac{\text{mL}}{\text{L}} \times \text{SVP concentration } \left(\frac{\text{mg}}{\text{mL}}\right)}$$

OR

When a specific SVP maximum dose is expressed in mL/kg/day (dose volume):

$$\text{IAE (mcg/kg/day)} = \frac{\text{Al concentration } \left(\frac{\text{mcg}}{\text{L}}\right) \times \text{SVP max. daily dosage (mL/kg/day)}}{1000\ \frac{\text{mL}}{\text{L}}}$$

1. Zinc Chloride

Zinc chloride ($ZnCl_2$) injection, USP contains 1 mg/mL zinc. The recommended maximum daily dosage is 0.3 mg/kg/day. The aluminum concentration is less than or equal to 150 mcg/L.

[14] Note that the concentration of the drug (i.e., SVP concentration (milligram/milliliter (mg/mL)) in formulas) and the prescribed maximum daily dosage of the drug product (i.e., SVP max. dosage (mg/kg/day) in formulas) should be expressed consistently in the same form, for example, active moiety, salt, or inorganic counter ion (see examples in Section IV.A.).

The derived aluminum exposure (IAE of zinc chloride) is calculated as the following:

IAE_{ZnCl2} (mcg/kg/day) = (150 mcg/L x 0.3 mg/kg/day) ÷ (1000 mL/L x 1 mg/mL) = 0.045 mcg/kg/day

2. Multiple Vitamins Injection

The following example pertains to multiple vitamins injection intended for pediatric patients.

The recommended dosages are expressed as mL/day and are weight-based. Among the range of body weights for pediatric patients in the dosing instructions, the maximum potential dosage is 3.25 mL/kg/day. The derived aluminum exposure (IAE of multiple vitamins injection) from the known labeled aluminum concentration (i.e., less than or equal to 30 mcg/L) is as follows:

$IAE_{multiple\ vitamins\ injection}$ (mcg/kg/day) = (30 mcg/L x 3.25 mL/kg/day) ÷ 1000 mL/L = 0.1 mcg/kg/day

3. Cysteine Hydrochloride

Cysteine hydrochloride (cysteine HCl) injection, USP contains 34.5 mg/mL of cysteine. The recommended maximum daily dosage is 15 mg cysteine/gram of amino acid (AA), with 4 g AA/kg/day in pediatric patients. The aluminum concentration is less than or equal to 120 mcg/L. The derived aluminum exposure (IAE of cysteine hydrochloride) from the known labeled aluminum concentration (i.e., less than or equal to 120 mcg/L) is calculated as follows:

$IAE_{cysteine\ HCl}$ (mcg/kg/day) = (120 mcg/L x 15 mg/g AA x 4 g AA/kg/day) ÷ (1000 mL/L x 34.5 mg/mL) = 0.21 mcg/kg/day

B. Calculation of the ACL Based on a Selected IAE_{SVP} for SVPs Under Development

For SVPs in development, the ACL in the drug product should be calculated using a selected IAE_{SVP} of 0.6 mcg/kg/day or lower. Hypothetical examples are presented below using the recommended dosages and drug (nutrient) concentrations.

1. Zinc Chloride

Zinc chloride injection contains 1 mg/mL zinc. The recommended maximum daily dosage is 0.3 mg/kg/day. The safety assessment of aluminum in PN is based on aluminum dose expressed as mcg/kg/day, with the IAE_{SVP} selected as 0.6 mcg/kg/day.

The ACL is calculated as follows:

$$\text{ACL (mcg/L)} = \frac{\frac{1000\ \text{mL}}{\text{L}} \times \left(\frac{\frac{0.6\ \text{mcg}}{\text{kg}}}{\text{day}} \times 1\text{mg of zinc/mL}\right)}{\frac{0.3\ \text{mg}}{\text{kg}}/\text{day}} = 2000\ \text{mcg/L}$$

An IAE_{SVP} value less than 0.6 mcg/kg/day can also be selected. The example given below is based on the selection of 0.3 mcg/kg/day as the IAE_{SVP}, which would reduce the potential for exceeding the TAE (more than 5 mcg/kg/day), particularly in patients who need more than five SVPs in their PN mixture. This approach results in the following calculation of the ACL for zinc chloride injection:

$$\text{ACL (mcg/L)} = \frac{\frac{1000\ \text{mL}}{\text{L}} \times \left(\frac{\frac{0.3\ \text{mcg}}{\text{kg}}}{\text{day}} \times 1\text{mg of zinc/mL}\right)}{\frac{0.3\ \text{mg}}{\text{kg}}/\text{day}} = 1000\ \text{mcg/L}$$

2. Cysteine Hydrochloride

The clinical dose of cysteine is determined by amino acid dose (e.g., mg cysteine/gram AA), therefore the formula below accommodates the amino acid dose:[15]

$$\text{ACL (mcg/L)} = \frac{1000 \times IAE\left(\frac{\frac{\text{mcg}}{\text{kg}}}{\text{day}}\right) \times \text{cysteine concentration}_{(\text{mg/mL})}}{\text{dose}\left(\frac{\text{mg}}{\text{gram}}\ AA\right) \times \text{dosage}_{\ AA\ \left(\frac{\text{grams}}{\text{kg}}/\text{day}\right)}}$$

The formula includes the following assumptions:

- IAE_{SVP} cysteine hydrochloride = 0.6 mcg/kg/day
- Clinical dose of cysteine base = 15 mg cysteine/gram AA
- Clinical dosage of amino acid = 4 grams/kg/day
- Cysteine concentration = 34.5 mg/mL

$$\text{ACL}\left(\frac{\text{mcg}}{\text{L}}\right) = \frac{1000\frac{\text{mL}}{\text{L}} \times \frac{\frac{0.6\text{mcg}}{\text{kg}}}{\text{day}} \times \frac{34.5_{\text{mg}}}{\text{mL}}}{15\frac{\text{mg}}{\text{gramAA}} \times 4\frac{\text{grams}}{\text{kg}}} = 345\ \text{mcg/L}$$

[15] Cysteine concentration in the formula is the concentration of the cysteine base in the drug product.

Note that the use of a higher cysteine concentration will result in a higher ACL because the ACL is proportional to the concentration of cysteine in the drug product.

An example of an acceptable approach would be the selection of 0.4 mcg/kg/day as the IAE_{SVP} because it would reduce the potential for exceeding the TAE (more than 5 mcg/kg/day), particularly in patients who need more than five SVPs in their PN mixture. This approach results in the following calculation of the ACL:

$$ACL\ \left(\frac{mcg}{L}\right) = \frac{1000\frac{mL}{L}\ x\ \frac{0.4 mcg}{kg}{day}\ x\ \frac{34.5_{mg}}{mL}}{15\frac{mg}{gramAA}\ x\ 4\frac{grams}{kg}} = 230\ mcg/L$$

V. MANUFACTURING CONSIDERATIONS FOR THE CONTROL OF ALUMINUM CONTAMINATION IN SVPS

Control of elemental impurities to ensure that the levels do not exceed the PDE is one part of the overall control strategy for a drug product. ICH Q3D(R2) provides general recommendations for risk assessment and control of elemental impurities. ICH Q3D(R2) does not provide recommendations of the actual values of the established PDE for some elemental impurities including aluminum for several reasons, including the differences in regulations and practices among geographic regions. Applicants and manufacturers must use validated assay methods to determine the aluminum content in PN. The assay methods must comply with current good manufacturing practice requirements.[16] Sponsors and applicants should establish the appropriate acceptance criterion of the aluminum content in an SVP based on the following two factors:

1) The historical experience of the manufacturing capability, such as pharmaceutical development, batch records, and results from release and stability studies of the registration batches

2) The dosing regimen for patients with renal impairment including preterm neonates

Sponsors and applicants should include information on these factors and how they inform the acceptance criteria in the product specifications of SVP at release and at expiry. Changes to product specifications generally must be submitted in a prior approval supplement (see section VI below).

For each SVP intended to be added to the PN admixture, the aluminum exposure to patients with renal impairment should not exceed the IAE. Therefore, the concentration of the aluminum impurity of each SVP should be controlled at or below the recommended ACL (see the calculation of ACL in section IV.B.). This information can be used to guide the establishment of the acceptance criterion for aluminum content in the SVP specification. If the historically observed maximum level of aluminum exceeds the calculated ACL using the methods shown in

[16] 21 CFR 201.323 (f).

this guidance, applicants and sponsors should develop mitigation and control strategies to reduce the aluminum contamination in the drug product (e.g., formulation design optimization, raw material and component controls, manufacturing process improvement, selection of appropriate container and closure system).

Regarding ANDAs, applicants should provide adequate justification to demonstrate that the proposed acceptance criterion is appropriate. Differences in the acceptance criterion of the aluminum content in the drug product specifications between a proposed ANDA and its reference listed drug product may be appropriate if adequately justified.

Manufacturers should work to minimize aluminum contamination in SVPs during the drug product development and product life cycle. For example, minerals are commonly added into USP Type I glass as modifiers and stabilizers to produce glass containers with desired physical properties and durability. Aluminum and other elemental impurities could leach into the SVP from the glass containers over time, especially for drug products with an extreme pH. Therefore, the pH of the formulation should be considered when performing risk assessment to identify the source and control of aluminum and other elemental impurities in SVPs.

As part of the risk mitigation, the control of aluminum should be considered in the proposed quality target product profile (e.g., route of administration, patient population, drug product formulation design, strength, primary packaging materials). As illustrated in the SVP ACL calculation formula in section III.B. and examples in section IV.B., the ACL is proportional to the active pharmaceutical ingredient (API) concentration for an individual SVP if the maximum daily dose of the SVP and its IAE remains unchanged. Under such a circumstance, a higher aluminum concentration resulting from a higher ACL will be anticipated when an applicant has selected a higher API concentration during the SVP formulation design. FDA encourages the applicant to discuss the aluminum control strategy with FDA's review divisions when developing SVPs intended to be a component of PN.[17] Finally, the applicant should also implement an adequate control strategy for postapproval changes that could affect aluminum content in the drug product during its life cycle.

VI. REGULATORY CONSIDERATIONS FOR THE CONTROL OF ALUMINUM CONTAMINATION IN SVPS

Applicants of approved or marketed NDAs or ANDAs for SVPs should conduct a risk assessment of their products and control aluminum according to the principles in this guidance once it is finalized. Confirmatory testing and submission of changes to the application should be concluded within 2 years of publication of a final guidance. Changes in specifications from those in the approved application must be submitted in a prior approval supplement unless otherwise

[17] When the submission is for an NDA, the applicant should contact the specific drug product review division with questions. When the submission is for an ANDA, the applicant should submit questions via the controlled correspondence pathway or via the pre-ANDA meeting request pathway. See the guidances for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (October 2022) and *Controlled Correspondence Related to Generic Drug Development* (March 2024). See also recommendations in the guidance for industry *Changes to an Approved NDA or ANDA* (April 2004).

exempted by regulation.[18] Generally, any drug product batch found to contain unacceptable levels of aluminum should not be released by the drug product manufacturer for distribution and may warrant removal from the market because such drug products may be considered adulterated under section 501 of the Federal Food, Drug, and Cosmetic Act (FD&C Act). FDA may exercise enforcement discretion when warranted to prevent or mitigate a shortage of a drug.

If any manufacturing changes or recalls related to aluminum contamination in SVPs are likely to lead to a meaningful disruption in the drug supply, applicants should contact CDER's Drug Shortage Staff at drugshortages@fda.hhs.gov to help meet obligations to report discontinuances or interruptions in their drug manufacture[19] and allow FDA to consider what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on the affected SVP.

VII. LABELING CONSIDERATIONS

A. Prescribing Information

1. Limitations of Use in the Indications and Usage Section

If there is a reasonable concern or uncertainty about the use of the SVPs or LVPs in a subpopulation because of the risk of aluminum toxicity, the INDICATIONS AND USAGE section can include limitations of use.[20] The following is an example:

> Limitations of Use
> The use of DRUG-X for parenteral nutrition in pediatric patients less than 1 year old is not recommended due to the risk of aluminum toxicity *[see Warnings and Precautions (5.x) and Use in Specific Populations (8.4)]*.

2. Warnings and Precautions Section

The WARNINGS AND PRECAUTIONS section for SVPs and LVPs must contain the following statement that should be included within a subsection entitled *Aluminum Toxicity* or with a similar subsection title:[21]

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[18] See 21 CFR 314.70(b)(2).

[19] See section 506C of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR 314.81(b)(3)(iii).

[20] See the draft guidance for industry *Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (July 2018). When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[21] 21 CFR 201.323(e). In this statement the term *µg* is a symbol for microgram. The Institute for Safe Medication Practices (ISMP) stated that the term *µg* has been frequently misinterpreted and involved in medication errors; therefore, ISMP and FDA recommend that the term *mcg* be used instead of *µg*. See ISMP's List of Error-Prone Abbreviations, available at https://www.ismp.org/recommendations/error-prone-abbreviations-list.

> WARNING: This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum.
>
> Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 µg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.

For LVPs, the WARNINGS AND PRECAUTIONS section must state that the drug product contains no more than 25 µg/L of aluminum.[22]

The WARNINGS AND PRECAUTIONS section must describe the limitations in use imposed by clinically significant adverse reactions[23] and should include steps to take to decrease the likelihood, shorten the duration, or minimize the severity of an adverse reaction.[24] For SVPs and LVPs, the WARNINGS AND PRECAUTIONS section should include a cross-reference to the DESCRIPTION section that includes a statement regarding the amount of aluminum in the drug product. For SVPs and LVPs with a total admixed aluminum content of no more than 4 to 5 mcg/kg/day, the following is an example of how to include such information in the *Aluminum Toxicity* subsection:[25]

> Exposure to aluminum from DRUG-X at the recommended dosage is not more than Y[26] mcg/kg/day *[see Dosage and Administration (2.x) and Description (11)]*.
>
> When prescribing DRUG-X for use in parenteral nutrition solutions containing other small volume parenteral products and/or pharmacy bulk packages, limit the total daily patient exposure to aluminum in the admixture to no more than 5 mcg/kg/day *[see Use in Specific Populations (8.4)]*.

The following is an example of how to include information in the *Aluminum Toxicity* subsection[27] when SVPs or LVPs are approved in one subpopulation (e.g., patients 1 year of age and older) when the total aluminum exposure does not exceed 4 to 5 mcg/kg/day, but use is not

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[22] 21 CFR 201.323(b). In this statement, FDA recommends use of the term *mcg* instead of *µg*. See footnote #21.

[23] 21 CFR 201.57(c)(6)(i).

[24] See the guidance for industry *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format* (October 2011).

[25] A similar subsection title may be used.

[26] Y equals IAE_{SVP} and is determined from calculations described above in this guidance (see section IV. A. of this guidance).

[27] A similar subsection title may be used.

recommended in another subpopulation (e.g., patients younger than 1 year of age) because of the risk of aluminum toxicity (the total aluminum exposure exceeds 5 mcg/kg/day in the subpopulation):

> When prescribing DRUG-X for use in parenteral nutrition solutions (containing other small volume parenteral products and/or pharmacy bulk packages) in adults and pediatric patients 1 year of age and older, limit the total daily patient exposure to aluminum in the admixture at no more than 4 to 5 mcg/kg/day. The use of DRUG-X for parenteral nutrition is not recommended in pediatric patients less than 1 year of age due to the risk of aluminum toxicity *[see Use in Specific Populations (8.4)]*.

3. Pediatric Use Subsection in the Use in Specific Populations Section

If a drug product is approved for use in pediatric patients (either all pediatric patients or in a specific pediatric age group or groups), the *Pediatric Use* subsection in the USE IN SPECIFIC POPULATIONS section must include information about specific risks or safety concerns (hazards) associated with the use of the drug product in pediatric patients or a specific pediatric age group (e.g., infants).[28] The following is an example of aluminum toxicity information for SVPs or LVPs in this subsection:

> DRUG-X contains aluminum that may be associated with central nervous system and bone toxicity. Preterm infants and pediatric patients up to 2 years of age receiving prolonged parenteral nutrition treatment with DRUG-X may be at higher risk for aluminum toxicity due to multiple factors, including immature renal function *[see Warnings and Precautions (5.x)]*.

If the use of the drug product for an indication not approved in pediatric patients is associated with a risk or safety concern (hazard) in pediatric patients, the risk or safety concern must be described in the *Pediatric Use* subsection.[29] The following is an example of aluminum toxicity information for SVPs and LVPs when the use of the drug product in pediatric patients is based on age:[30]

> DRUG-X contains aluminum that may be associated with central nervous system and bone toxicity. The safety and effectiveness of DRUG-X (for Indication-Y) have not been established in pediatric patients younger than Z years old, and the use of DRUG-X for parenteral nutrition is not recommended in this age group due to the risk of aluminum toxicity *[see Warnings and Precautions (5.x)]*.

[28] 21 CFR 201.57(c)(9)(iv)(B), (C), and (D).

[29] 21 CFR 201.57(c)(9)(iv)(E) or (F).

[30] The use of the drug product in pediatric patients because of aluminum toxicity may alternatively be based on weight.

4. Description Section

For SVPs or LVPs, the DESCRIPTION section should contain a statement regarding the amount of aluminum in the drug product. The following is an example of this statement:

> DRUG-X contains no more than Y mcg/L of aluminum *[see Warnings and Precautions (5.x)]*.

If the SVP is a lyophilized powder (*for injection* dosage form), this section should state the following:

> After reconstitution, the aluminum concentration will be no more than Y mcg/L.

However, if the maximum level of aluminum in one of the lyophilized powder SVPs is 25 mcg/L or less, instead of stating the exact amount of aluminum, this section can state the following:

> After reconstitution, the aluminum concentration will be no more than 25 mcg/L.

B. Container Label and Carton Labeling

1. SVPs

The maximum level of aluminum present at expiry must be stated on the immediate container label and carton labeling[31] of all SVPs as follows:[32] "Contains no more than X µg/L of aluminum." However, if the maximum level of aluminum in one of these SVPs is 25 mcg/L or less, instead of stating the exact amount of aluminum, the immediate container label and carton labeling may state the following:[33] "Contains no more than 25 µg/L of aluminum."

If the SVP is a lyophilized powder (*for injection* dosage form), the immediate container label and carton labeling must state the following:[34] "When reconstituted in accordance with the package insert instructions, the concentration of aluminum will be no more than X µg/L." However, if the

[31] According to section 201(k) of the FD&C Act (21 U.S.C. 321(k)), "a requirement made by or under authority of this chapter that any word, statement, or other information appear on the label shall not be considered to be complied with unless such word, statement, or other information also appears on the outside container or wrapper, if any there be, of the retail package of such article, or is easily legible through the outside container or wrapper."

[32] 21 CFR 201.323(c). In this statement, FDA recommends use of the term *mcg* instead of *µg*. See footnote #21.

[33] 21 CFR 201.323(d). In this statement FDA recommends use of the term *mcg* instead of *µg*. See footnote #21.

[34] 21 CFR 201.323(c). In this statement FDA recommends use of the term *mcg* instead of *µg*. See footnote #21. FDA uses the term *Prescribing Information* rather than the term *package insert* to refer to labeling that meets the requirements of 21 CFR 201.56(d) and 21 CFR 201.57 (PLR format) and labeling that meets the requirements of 21 CFR 201.56(e) and 21 CFR 201.80 because the term *package insert* may also refer to other types of labeling in the package besides Prescribing Information, such as Medication Guides, Patient Package Inserts, and Instructions for Use. In this statement, FDA does not intend to object to the use of the term *Prescribing Information* instead of *package insert*.

maximum level of aluminum in one of these lyophilized powder products is 25 mcg/L or less, instead of stating the exact amount of aluminum, the immediate container label and carton labeling can state the following:[35] "When reconstituted in accordance with the package insert instructions, the concentration of aluminum will be no more than 25 µg/L."

This maximum level of aluminum in SVPs must be stated as the highest of one of the following:

a) The highest level for the batches produced during the last 3 years

b) The highest level for the latest five batches

c) The maximum historical level, but only until completion of production of the first five batches after July 26, 2004[36]

2. LVPs

As established in 21 CFR 201.323(a), aluminum content in LVPs must not exceed 25 mcg/L of aluminum. The maximum level of aluminum present at expiry should be stated on the immediate container label and carton labeling of all LVPs as "Contains no more than [X] mcg/L of aluminum" or, instead of stating the exact amount of aluminum, the immediate container label and carton labeling may state, "Contains no more than 25 mcg/L of aluminum."

[35] 21 CFR 201.323(d). In this statement FDA recommends use of the term mcg instead of µg. See footnote #21. FDA uses the term *Prescribing Information* rather than the term *package insert* to refer to labeling that meets the requirements of 21 CFR 201.56(d) and 21 CFR 201.57 (PLR format) and labeling that meets the requirements of 21 CFR 201.56(e) and 21 CFR 201.80 because the term *package insert* may also refer to other types of labeling in the package besides Prescribing Information, such as Medication Guides, Patient Package Inserts, and Instructions for Use. In this statement, FDA recommends use of the term *Prescribing Information* instead of *package insert*.

[36] 21 CFR 201.323(c).

GLOSSARY

Total aluminum exposure (TAE) (microgram/kilogram/day (mcg/kg/day)): The daily patient exposure to aluminum, from all components used in parenteral nutrition (PN) (SVPs and LVPs) therapy, not to exceed 5 mcg/kg/day (see Figure 1).

Individual aluminum exposure (IAE) (mcg/kg/day): The maximum daily patient exposure to aluminum from an individual component of PN (SVPs and LVPs) therapy; the value not to exceed is variable among individual drug products and is dependent on the component and composition of the PN admixture prescribed or intended for clinical use.

Aluminum content (mcg): The amount of aluminum present in a single dose of the individual drug product. It is derived from the aluminum concentration in the drug product.

Aluminum concentration (mcg/Liter (L)): The amount of aluminum per liter of the individual drug product determined from batch analyses.

Aluminum concentration limit (ACL) (mcg/L): The highest aluminum concentration established in each individual drug product that will ensure compliance with its individual IAE. It is the basis for the establishment of the acceptance criteria for elemental impurity aluminum in drug product specifications. The acceptance criteria should not exceed the recommended aluminum concentration limit for each drug product.

Drug product concentration (milligram/milliliter (mg/mL)): The amount of the drug expressed in milligram per milliliter of the individual drug product defined in an application.[1]

Large volume parenteral (LVP): A terminally sterilized aqueous drug product packaged in a single-dose container with a capacity of 100 milliliters or more, for use in PN in a human.

Maximum daily dosage (max. daily dosage) (mg or mL/kg/day): The prescribed maximum daily dosage of the specific drug[2] expressed per kilogram of the patient body weight.

Specification for drug product: A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described for the drug product.[3]

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[1] Note that the concentration of the drug (i.e., SVP concentration (mg/mL) in formulas) and the prescribed maximum daily dosage of the drug product (i.e., SVP max. dosage (mg/kg/day) in formulas) should be expressed consistently in the same form (e.g., the active moiety, salt, or inorganic counter ion).

[2] Ibid.

[3] See the ICH guidance for industry *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* (December 2000). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

Small volume parenteral (SVP): Refers to products packaged as single doses or as PBPs for use in PN in a container with a capacity of less than 100 milliliters or SVPs packaged as PBPs for use in PN.

ABBREVIATIONS AND ACRONYMS

AA	amino acid
ACL	aluminum concentration limit
Al	aluminum
ANDA	abbreviated new drug application
API	active pharmaceutical ingredient
CFR	Code of Federal Regulations
FDA	Food and Drug Administration
FD&C Act	Federal Food, Drug, and Cosmetic Act
IAE	individual aluminum exposure
IAE_{LVP}	individual aluminum exposure from large volume parenteral
$IAE_{LVPtotal}$	total aluminum exposure from large volume parenterals
IAE_{SVP}	individual aluminum exposure from small volume parenteral
$IAE_{SVPtotal}$	total aluminum exposure from small volume parenterals
ICH	International Council for Harmonisation
ISMP	Institute for Safe Medication Practices
kg	kilogram
L	liter
LVP	large volume parenteral
mEq	milliequivalent
mcg	microgram
mL	milliliter
NDA	new drug application
NMT	no more than
PBP	pharmacy bulk package
PDE	permitted daily exposure
PLR	physician labeling rule
PN	parenteral nutrition
SVP	small volume parenteral
TAE	total aluminum exposure
TPN	total parenteral nutrition
USP	United States Pharmacopeia

REFERENCES

LITERATURE

Arnold CJ, GG Miller, and GA Zello, 2003, Parenteral Nutrition-Associated Cholestasis in Neonates: The Role of Aluminum, Nutr Rev, 61(9):306–310.

Bishop NJ, R Morley, JP Day, and A Lucas, 1997, Aluminum Neurotoxicity in Preterm Infants Receiving Intravenous-Feeding Solutions, N Engl J Med, 336(22):1557–1561.

Bohrer D, PC do Nascimento, R Binotto, and E Becker, 2003, Influence of the Glass Packing on the Contamination of Pharmaceutical Products by Aluminium. Part III: Interaction Container-Chemicals During the Heating for Sterilisation, J Trace Elem Med Biol, 17(2):107–115.

Bohrer D, PC do Nascimento, R Binotto, and R Carlesso, 2001, Influence of the Glass Packing on the Contamination of Pharmaceutical Products by Aluminium. Part II: Amino Acids for Parenteral Nutrition, J Trace Elem Med Biol, 15(2-3):103–108.

Bohrer D, PC do Nascimento, R Binotto, E Becker, and S Pomblum, 2002, Contribution of the Raw Material to the Aluminum Contamination in Parenterals, JPEN J Parenter Enteral Nutr, 26(6):382–388.

Boyce BF, GS Fell, HY Elder, BJ Junor, HL Elliot, G Beastall, I Fogelman, and IT Boyle, 1982, Hypercalcaemic Osteomalacia Due to Aluminium Toxicity, Lancet, 2(8306):1009–1013, doi: 10.1016/s0140-6736(82)90049-6. PMID: 6127501.

Fewtrell MS, NJ Bishop, CJ Edmonds, EB Isaacs, and A Lucas, 2009, Aluminum Exposure From Parenteral Nutrition in Preterm Infants: Bone Health at 15-Year Follow-up, Pediatrics, 124(5):1372–1379.

Finberg L, HS Dweck, F Holmes, and N Kretchmer, 1986, American Academy of Pediatrics Committee on Nutrition: Aluminum Toxicity in Infants and Children, Pediatrics, 78(6):1150–1154.

Gilbert-Barness E, LA Barness, J Wolff, and C Harding, 1998, Aluminum Toxicity, Arch Pediatr Adolesc Med, 152(5):511–512.

Klein GL, AM Leichtner, and MB Heyman, 1998, Aluminum in Large and Small Volume Parenterals Used in Total Parenteral Nutrition: Response to the Food and Drug Administration Notice of Proposed Rule By the North American Society for Pediatric Gastroenterology and Nutrition, J Pediatr Gastroenterol Nutr, 27(4):457–460.

Klish WJ, SS Baker, CA Flores, MK Georgieff, AM Lake, RL Leibel, JN Udall Jr., M Cheney, PN Daniels, SS Harris, VS Hubbard, E Levin, A Prendergast, AE Smith, E Yetley, R Yip, S Zlotkin, RM Lauer, and EF Bell, 1996, Aluminum Toxicity in Infants and Children, American Academy of Pediatrics, Committee on Nutrition, Pediatrics, 97(3):413–416.

Larchet M, P Chaumont, M Galliot, R Bourdon, O Goulet, and C Ricour, 1990, Aluminium Loading in Children Receiving Long-Term Parenteral Nutrition, Clin Nutr, 9(2):79–83.

Poole RL, KP Pieroni, S Gaskari, TK Dixon, KT Park, and JA Kerner Jr., 2011, Aluminum in Pediatric Parenteral Nutrition Products: Measured Versus Labeled Content, J Pediatr Pharmcol Ther, 16(2):92–97.

United States Pharmacopeia (USP) Chapters

USP General Chapter <7> Labeling

USP General Chapter <659> Packaging and Storage Requirements

USP General Chapter <1660> Evaluation of the Inner Surface Durability of Glass Containers

Guidances for Industry[1]

Draft guidance for industry *Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (July 2018)[2]

Guidance for industry *Controlled Correspondence Related to Generic Drug Development* (March 2024)

Guidance for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (October 2022)

Guidance for industry *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format* (October 2011)

ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) guidance for industry *E11 (R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population* (April 2018)

ICH guidance for industry *Q2(R2) Validation of Analytical Procedures* (March 2024)

ICH guidance for industry *Q3D(R2) Elemental Impurities* (September 2022)

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[2] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

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716 ICH guidance for industry *Q6A Specifications: Test Procedures and Acceptance Criteria for*
717 *New Drug Substances and New Drug Products: Chemical Substances* (December 2000)