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DRAFT GUIDANCE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)

December 2022
Clinical/Medical

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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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 in parenteral nutrition (PN)[2] represents a major safety concern, necessitating that PN products meet the requirements in 21 CFR 201.323 for aluminum content and labeling. Per the regulation, aluminum content of large volume parenteral (LVP) drug products[3] used in total parenteral nutrition (TPN) therapy must not exceed 25 micrograms per liter (mcg/L).[4] In contrast, the limits for the aluminum content of small volume parenteral (SVP) drug products and pharmacy bulk packages (PBPs)[5] used in PN are not specified by statute or regulation.

[1] This guidance has been prepared by the Division of Hepatology and Nutrition in cooperation 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] *Parenteral nutrition* encompasses both total parenteral nutrition and peripheral parenteral nutrition, administered via central or peripheral veins. FDA understands that 21 CFR 201.323 refers only to "total parenteral nutrition;" however, based on current clinical practice, the Agency believes that it is appropriate to treat the terms *total parenteral nutrition, peripheral parenteral nutrition*, and *parenteral nutrition* interchangeably for the purposes of this guidance.

[3] 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 in a human.

[4] 21 CFR 201.323(a).

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

Further, the International Council for Harmonisation (ICH) has not established a permitted daily exposure (PDE) for aluminum.[6]

To address this lack of information, this guidance clarifies the key factors in determining the aluminum content in an SVP drug product[7] and/or a PBP intended as a component of PN and provides FDA's recommendations regarding the aluminum concentration limits in SVP drug products[8] and PBPs for PN.

Additionally, this guidance is intended to assist applicants in determining the appropriate content and placement of information on aluminum in SVP and PBP human prescription drug product labeling,[9] including the Prescribing Information and container label and carton labeling. The intent of this guidance is to help assure that the information is clear and accessible to health care practitioners and guides the safe and effective use of the drug product.

The recommendations in this guidance apply to the evaluation of aluminum content and establishment of a recommended aluminum concentration limit in an SVP drug product or PBP for PN.[10]

The guidance does not alter labeling considerations or recommended concentration limits for aluminum content in LVP drug products for TPN as those are already addressed in 21 CFR 201.323. However, because LVP and SVP drug products can be used together in PN therapy, this

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[6] PDE is defined as the maximum acceptable intake of elemental impurity in pharmaceutical products per day. See the ICH guidance for industry *Q3D(R1) Elemental Impurities* (March 2020). The ICH guidance does not provide a PDE for aluminum because of differences in regulations and practices among geographic regions. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[7] For the purposes of this guidance, references to *drug products* include drug products approved under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355) that are subject to section 503(b)(1) of the FD&C Act (21 U.S.C. 353(b)(1)).

[8] For the purposes of this guidance, use of the term *SVP drug products* includes both SVP drug products and SVP drug products packaged as PBPs, unless otherwise noted.

[9] See 21 CFR 201.56(d) and 21 CFR 201.57. The labeling examples in this guidance are for prescription SVP and PBP drug products 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 for SVP drug products with labeling that meets the requirements of 21 CFR 201.56(e) and CFR 201.80 (*old format*) with the FDA prescription drug review division. For new drug applications that are not required to have labeling in PLR format, applicants can consider voluntarily converting the 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 makes Prescribing Information more accessible for use with electronic prescribing tools and other electronic information resources.

[10] The recommendations in this guidance apply to all prescription drug products that are the subject of new drug applications (NDAs), abbreviated new drug applications (ANDAs), and future supplements to those applications; however, the labeling recommendations in section VI. of this guidance only apply to NDAs and supplemental NDAs. The recommendations in this guidance do not apply to compounded drug products or nonprescription drug products.

guidance does consider the aluminum content in LVP drug products when calculating the recommended aluminum concentration limit in an SVP drug product.

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. SVP drug products for PN are used as additives to 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 1 percent of ingested aluminum to be absorbed into the bloodstream, and renal excretion removes 99 percent of that aluminum. Despite that, aluminum toxicity has been documented in medical literature for more than 30 years,[11] with manifestations that include osteomalacia and reduced bone mineralization, neurological dysfunction and dialysis encephalopathy, microcytic hypochromic anemia, and cholestasis.

A long-implicated, major source of aluminum exposure is PN, resulting from contamination of ingredients. PN ingredients are contaminated with aluminum in raw materials as well as through byproducts from the manufacturing process and packaging system, during which 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. Patients with underlying renal impairment who receive prolonged courses of PN support 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 often require many days of PN support are at particularly high risk.

Research indicates that patients with renal impairment, including preterm neonates, who receive parenteral levels of aluminum at greater than 4 to 5 micrograms/kilogram/day (mcg/kg/day) accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue

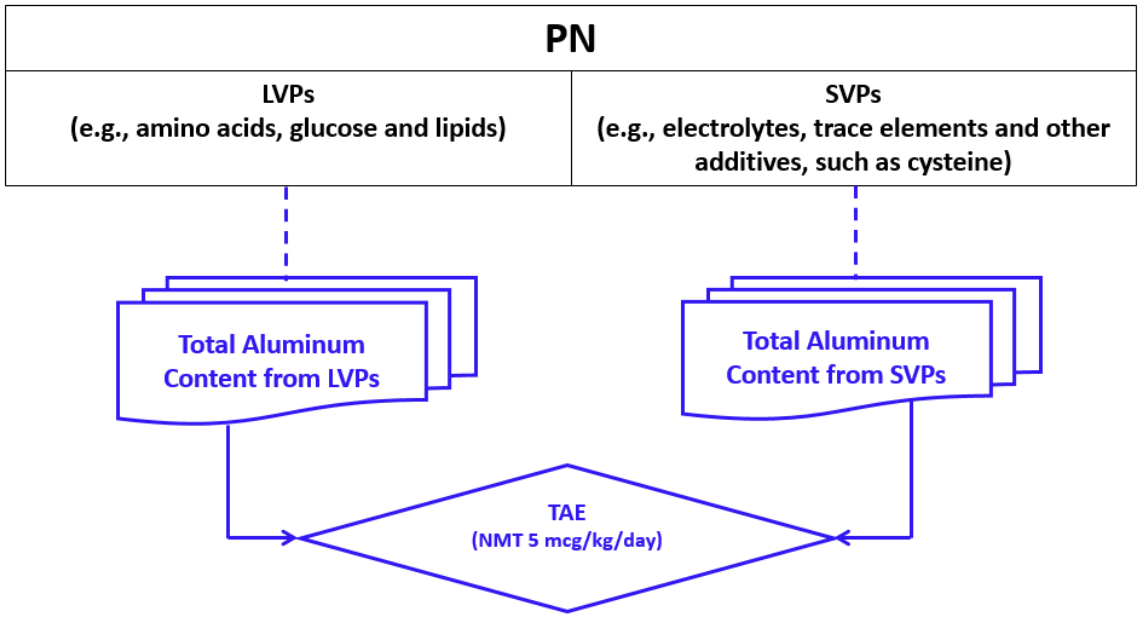
[11] See, for example, Boyce BF, GS Fell, HY Elder, BJ Junor, HL Elliot, G Beastall, I Fogelman, and IT Boyle, 1982, Hypercalcaemic Osteomalacia Due to Aluminium Toxicity, Lancet, 2(8306):1009–1013, doi: 10.1016/s0140-6736(82)90049-6. PMID: 6127501.

[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.

loading may occur at even lower rates of administration.[13] Despite these potential risks and the variability of each SVP drug product added to PN for individual patients, patients with renal impairment benefit from PN. Because patients with renal impairment, including all preterm neonates, comprise a major portion of those requiring PN support, FDA recommends that the total aluminum exposure (TAE) from PN uniformly should not exceed 5 mcg/kg/day to protect the safety of all patients.

Multiple sources of LVP and SVP drug products comprise PN, and each drug product may contribute to the total aluminum content of PN, which should not exceed 5 mcg/kg/day (see Figure 1). Applicants should consider the recommended limit of aluminum in individual SVP drug products as the drug product's contribution to the total daily aluminum dose from PN to determine whether the total daily exposure exceeds 5 mcg/kg/day.

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 ALUMINUM CONCENTRATION LIMIT IN THE SVP DRUG PRODUCT

There are two major steps in deriving the aluminum concentration limit (ACL) in an SVP drug product for PN. First, the applicant needs to determine the individual aluminum exposure (IAE) of the individual SVP drug product (see section IV. A., Determination of IAE_{SVP} of Drug Products with Known or Labeled Aluminum Concentration); then, the applicant can use the IAE to calculate the ACL (see section IV. B., Determination of ACL from IAE_{SVP} for SVP Drug Product Under Development) for each specific SVP drug product.

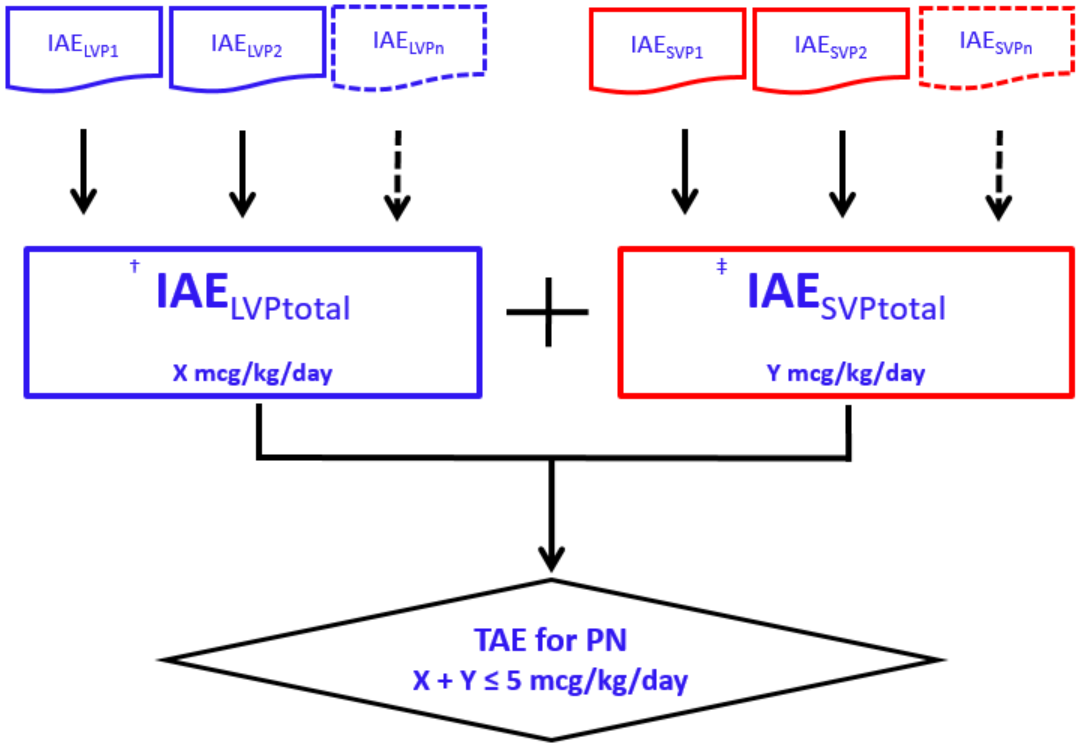
[13] 21 CFR 201.323(e).

A. Determination of the IAE of Individual SVP Drug Products

The first step in the derivation of the ACL in the specific SVP drug product is the determination of the IAE for the individual SVP drug product.

The determination of the IAE from each individual LVP and SVP drug product combined into the final PN is needed to determine whether the total daily aluminum dose from the PN therapy exceeds 5 mcg/kg/day (see Figure 2 and examples below).

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 LVP drug products; IAE$_{SVP}$ = individual aluminum exposure from SVP drug product; IAE$_{SVPtotal}$ = total aluminum exposure from SVP drug products

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

‡ IAE$_{SVP}$ = Y mcg/kg/day divided by the number of SVP drug products intended for use in the PN therapy. When dividing the total aluminum contribution from SVP drug products (Y mcg/kg/day) by the number of SVP drug products intended for use in the PN therapy, an equal contribution of IAE from each SVP drug product is assumed when the IAE$_{SVP}$ for the drug products are unknown. This calculation can be modified based on known or established values of IAE$_{SVP}$ for a given drug product, and the number of SVP additives in a typical PN prescription (e.g., four to six) can be justified for each SVP drug product indication.

- **TAE from LVP drug product (X mcg/kg/day or $IAE_{LVPtotal}$)**

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

  — The aluminum concentration in each LVP component used in a TPN therapy must not exceed 25 mcg/L.[14] 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 on daily dose volume of 80 mL/kg/day of $LVP_{1+2+n,}$ the total aluminum contribution from an LVP drug product (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 will receive 6 mcg/day (i.e., $IAE_{LVPtotal}$ times 3 kg) of aluminum from the LVP drug product.

- **TAE from SVP drug product (Y mcg/kg/day or $IAE_{SVPtotal}$)**

  — TAE from SVP drug products can be calculated by subtracting the $IAE_{LVPtotal}$ aluminum contribution from the TAE for the total amount of PN therapy (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 drug product ($IAE_{LVPtotal}$) 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 3 mcg/kg/day ($IAE_{SVPtotal}$).

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

  — IAE from an individual SVP drug product (IAE_{SVP}) should take into consideration the number of SVP drug products intended to be used in the PN therapy, and the known IAE_{SVP} of other individual SVP drug products intended for use in the PN therapy. If the aluminum content of an individual SVP drug product is not known, the applicant should consider equal contribution of IAE from each indivudal SVP drug product. Based on current FDA experience, a typical PN prescription can include approximately four to six SVP additives, but this can vary depending on the specific SVP drug product indication and/or PN prescription practice trends. The applicant should provide a rationale or justification for the number of SVP additives used in determining the IAE.

  Example: If total aluminum exposure from SVP drug products (Y) is 3 mcg/kg/day ($IAE_{SVPtotal}$), and if six SVP additives are used, IAE for each individual SVP drug

[14] See 21 CFR 201.323(a).

product should not exceed 0.5 mcg/kg/day assuming an equal contribution of IAE from each individual SVP drug product.

— When the specific IAE_{SVP} is known for a given SVP drug product, the calculation can be adjusted to ensure that the Y does not exceed 3 mcg/kg/day.

Example: Table 1 lists the known IAE_{SVP} for potassium acetate as less than or equal to 0.6 mcg/kg/day. By subtracting the known IAE_{SVP} of potassium acetate (i.e., 0.6 mcg/kg/day) from the $IAE_{SVPtotal}$ (or Y mcg/kg/day, i.e., 3 mcg/kg/day), the total aluminum contribution from the remaining five individual SVP drug products would be 2.4 mcg/kg/day. Individual IAE_{SVP} for the five remaining SVP drug products can be estimated as less than or equal to 0.48 mcg/kg/day.

B. Determination of the ACL in an SVP Drug Product

Once the IAE for an individual SVP drug product is determined and adequately justified, the proposed IAE can be used to calculate the ACL in mcg/L for each specific SVP drug product as shown in the formula below.

$$\text{SVP ACL (mcg/L)} = 1000\frac{\text{mL}}{\text{L}} \text{ x } \left(\frac{\text{IAE (mcg/kg/day) x SVP conc. (mg/mL)}}{\text{SVP max. daily dosage (mg/kg/day)}}\right)^{15}$$

The acceptance criteria of the aluminum concentration in the SVP drug product 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 DETERMINATION OF IAE AND ACL

This section provides examples of the determination of IAE_{SVP} and/or SVP ACL of SVP drug products to include known or existing SVP drug products with known aluminum concentrations. Section A addresses the determination of IAE_{SVP} of SVP Drug Products with Known or Labeled Aluminum Concentration (Table 1), and Section B addresses the determination of ACL from IAE_{SVP} for an SVP Drug Product Under Development.

A. Determination of IAE_{SVP} of SVP Drug Products with Known or Labeled Aluminum Concentration

When there is an SVP drug product with a known or labeled aluminum concentration (Al conc. in formulas) (e.g., potassium acetate, multivitamins, zinc chloride, cysteine hydrochloride) (see Table 1 below), the projected aluminum exposure from the SVP drug product (mcg/kg/day) or

[15] Note that the concentration of the drug (i.e., SVP conc. (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, e.g., active moiety, salt, or inorganic counter ion (see examples in Table 1, Section IV. A.).

IAE_{SVP} of an individual drug product can be calculated (right column of Table 1) using the following formula when specific SVP maximum dose is expressed in milligram (mg)/kg/day:

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

or

When a specific SVP maximum dose is expressed in mL/kg/day (dose volume), the IAE_{SVP} of a specific drug product with a known or labeled aluminum concentration can be calculated (right column of Table 1) using the following formula:

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

Table 1. Examples of IAE_{SVP} from Individual SVP Drug Products with Known Aluminum Concentration

Drug Product Name	Drug Product Concentration	Maximum Daily Dosage	Labeled Aluminum Concentration Limit* (mcg/L)	IAE_{SVP} (mcg/kg/day)
Potassium Acetate	2 mEq/mL of Potassium	6 mEq/kg/day	NMT 200	≤0.6
Zinc Chloride	1 mg/mL of Zinc	0.3 mg/kg/day	NMT 150	≤0.045
Multiple Vitamins Injection	Multiple vitamins (not applicable)**	3.25 mL/kg/day	NMT 30	≤0.1
Cysteine Hydrochloride	34.5 mg/mL of cysteine	15 mg cysteine /g of AA***	NMT 120	≤0.21

IAE = individual aluminum exposure; SVP = small volume parenteral; IAE_{SVP} = individual aluminum contribution from SVP drug product; mcg = microgram; L = liter; kg = kilogram; mEq = milliequivalent; mL = milliliter; mg = milligram; g = gram; NMT= no more than, AA = amino acid.

* Known aluminum concentrations have been demonstrated to be no more than the labeled limit.

** Multivitamins injections are fixed-dose combination products, and the volume-based dosage is derived from the known concentrations of each component.

*** Maximum amino acid dose of 4 grams AA/kg/day.

1. Potassium Acetate

Potassium acetate (KOAc) injection contains 2 milliequivalents/milliliter (mEq/mL) potassium. The recommended dosage ranges are 40 to 80 mEq/day in adults, 2 to 3 mEq/kg/day in older pediatric patients, and 2 to 6 mEq/kg/day in neonates. The maximum weight-based dose (6

mEq/kg/day) should be used for calculations to support establishment of aluminum acceptance criteria. The derived aluminum exposure (IAE of potassium acetate) from the known labeled aluminum concentration (i.e., less than or equal to 200 mcg/L) is as follows:

IAE_{KOAC} (mcg/kg/day) = (200 mcg/L x 6 mEq/kg/day) ÷ (1000 mL/L x 2 mEq/mL) = 0.6 mcg/kg/day

2. Zinc Chloride

Zinc chloride ($ZnCl_2$) injection, United States Pharmacopeia (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.

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

3. Multiple Vitamins Injection

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

The recommended dosage levels 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

4. Cysteine Hydrochloride

Cysteine hydrochloride (cysteine HCl) injection, USP contains 34.5 mg/mL of cysteine. The recommended maximum daily dosage is 15mg 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. Determination of ACL from IAE_{SVP} for SVP Drug Product Under Development

For SVP drug products in development, the ACL in the drug product can be calculated using an estimated or known IAE_{SVP}.

Unless IAE_{SVP} of all drug products in the final PN admixture is known, sponsors should make assumptions for the IAE_{SVP} of the SVP drug product in development to determine ACL. The hypothetical examples below use marketed SVP drug products but assume that the aluminum concentration is not known to illustrate the calculation that would be conducted during development.

Depending on the assumptions made regarding the IAE_{SVP}, such as the number and the proportion of aluminum content of other concomitantly administered SVP PN components, ACL in a given drug product can vary widely. For the premarket development phase, the cysteine hydrochloride example (see section IV. B. 2., Cysteine Hydrochloride) illustrates the effect of the assumptions made regarding the number of and aluminum content of other individual SVP drug products administered together with PN.

1. Potassium Acetate

Potassium acetate injection contains 2 mEq/mL potassium. The recommended dosage ranges are 40 to 80 mEq/day in adults, 2 to 3 mEq/kg/day in older pediatric patients, and 2 to 6 mEq/kg/day in neonates. The safety assessment of aluminum in PN is based on aluminum dose expressed as mcg/kg/day.[16] For potassium acetate, the highest recommended potassium dosage on a body weight basis (expressed as mEq/kg/day) will deliver the highest aluminum dosage on a body weight basis (mcg/kg/day). Therefore, the applicant should use the maximum weight-based dosage of potassium (6 mEq/kg/day) for calculations to support the establishment of the ACL.

As described in section IV. A., Determination of IAE_{SVP} of Drug Products with Known or Labeled Aluminum Concentration, the $IAE_{SVPtotal}$ is calculated to be 3 mcg/kg/day, as follows:

$TAE - IAE_{LVPtotal} = IAE_{SVPtotal}$ (or $TAE - X = Y$)
5 mcg/kg/day – 2 mcg/kg/day = 3 mcg/kg/day

Based on the assumption that up to five SVP drug products (including potassium acetate) may be added to TPN therapy, with equal contribution of aluminum among the SVP drug products, the IAE for potassium acetate is calculated as follows:

$IAE_{SVPtotal} \div 5$ SVPs = IAE for individual SVP
3 mcg/kg/day ÷ 5 SVPs = 0.6 mcg/kg/day for individual SVP (potassium acetate)

Therefore, the assumed IAE_{SVP} of potassium acetate equals 0.6 mcg/kg/day.

The ACL is calculated as follows:

$$\text{ACL (mcg/L)} = \frac{\frac{1000\ \text{mL}}{\text{L}} \times \left(\frac{\frac{0.6\ \text{mcg}}{\text{kg}}}{\text{day}} \times 2\ \text{mEq of potassium/mL}\right)}{\frac{6\ \text{mEq}}{\text{kg}}/\text{day}} = 200\text{mcg/L}$$

[16] See 21 CFR 201.323(e).

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:

$$\text{ACL (mcg/L)} = \frac{1000 \text{ x IAE} \left(\frac{\text{mcg}}{\frac{\text{kg}}{\text{day}}}\right) \text{ x cysteine conc.}^{17}\ _{\text{(mg/mL)}}}{\text{cysteine max. daily dosage } \left(\frac{\text{mg}}{\text{gram}}\ _{\text{AA}}\right) \text{ x dose}\ _{\text{AA}\ (\frac{\text{grams}}{\text{kg}}\text{/day})}}$$

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 conc. = 34.5 mg/mL

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

Table 2 is the illustration of ACL in cysteine hydrochloride injection using the formula above with different IAE_{SVP} assumptions and cysteine hydrochloride concentrations (5 percent or 7.25 percent). Because the TAE is fixed *a priori*, increasing the IAE of each SVP drug product decreases the number of SVP additives that can be assumed.

On the other hand, the higher the concentration of cysteine, the higher ACL because it is proportional to the concentration of cysteine in the drug product.

[17] Cysteine conc. is the concentration of the cysteine base in the drug product.

Table 2. An Illustration of Calculation of Recommended ACL in Cysteine Hydrochloride Injection Based on the Maximum Daily Clinical Dose of Cysteine and Variations of IAEs, Drug Product Concentrations of Cysteine (5 percent or 7.25 percent), and Maximum Number of SVP Drug Products Allowed

Cysteine Daily Dosage	Amino Acid Daily Dosage	IAE of Each SVP Additive	ACL in Cysteine Hydrochloride Injection		N* (Max. number of SVP Additives)
			5%** (34.5 mg/mL of Cysteine)	7.25%** (50 mg/mL of Cysteine)	
(mg cysteine/g AA)/ day)	(g/kg/day)	(mcg/kg/day)	(mcg/L)	(mcg/L)	
15	4	0.1	58	83	30
15	4	0.6	345	500	5
15	4	1	575	833	3
15	4	3	1725	2500	1

Calculated numbers with a decimal place are rounded to the next integer.
ACL = aluminum concentration limit; IAE = individual aluminum exposure; SVP = small volume parenteral; AA = amino acid; mg = milligram; mL = milliliter; g = gram; kg = kilogram; mcg = microgram; L = liter; PN = parenteral nutrition; $IAE_{SVPtotal}$ = total aluminum exposure from SVP drug products.
*Assuming the total aluminum from SVP drug products in PN therapy, ($IAE_{SVPtotal}$), is 3 mcg/kg/day.
** Concentration based on amount of cysteine hydrochloride monohydrate.

V. MANUFACTURING CONSIDERATIONS FOR THE CONTROL OF ALUMINUM CONTENT IN SVP DRUG PRODUCTS

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. The International Council for Harmonisation (ICH) guidance for industry *Q3D(R1) Elemental Impurities* (March 2020) (ICH Q3D(R1)) provides general recommendations for risk assessment and control of elemental impurities. ICH Q3D(R1) does not provide recommendations of the actual values of the established PDE for some elemental impurities including aluminum because of several reasons, including the differences in regulations and practices among geographic regions. FDA recommends that applicants establish the tests for the aluminum content (i.e., concentration) with validated analytical methods and an appropriate acceptance criterion and include those in the specifications of SVP drug products for PN at release and at expiry. Applicants should establish the appropriate acceptance criterion of the aluminum content in an SVP drug product 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; and

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

For each SVP drug product intended to be added to the PN, the aluminum exposure to patients with renal impairment should not exceed the IAE. Therefore, the concentration of the aluminum

impurity of each SVP drug product should be controlled at or below the recommended ACL (see the determination of ACL in section IV.B., Determination of ACL from IAE_{SVP} for SVP Drug Product Under Development). This information can be used to guide the establishment of the acceptance criterion for aluminum content in the SVP drug product specification. If the historically observed maximum level of aluminum exceeds the calculated safety level per this guidance, FDA recommends developing mitigation and control strategies to reduce the aluminum content in a drug product (e.g., formulation design optimization, manufacturing process improvement, selection of appropriate container and closure system).

If there is adequate justification, the differences in the acceptance criterion of the aluminum content in the drug product specifications between the proposed abbreviated new drug application (ANDA) and the reference listed drug (RLD) product may be considered as permissible as part of the Agency's overall benefit-risk analysis of the ANDA at issue.

Some special consideration should be given in the control of aluminum impurities in SVP drug products 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 drug product from the glass containers over time, especially for drug products with a formulation at 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 SVP drug products. 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., the ACL is proportional to the API concentration for an individual SVP drug product if the maximum daily dose of the SVP drug product and its IAE remain unchanged. Under such 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 drug product formulation design. FDA encourages the applicant to discuss aluminum control strategy with FDA's review divisions when developing SVP drug products intended to be a component for TPN therapy.[18] Finally, the applicant should also implement an adequate control strategy for postapproval changes that could affect aluminum content in the drug product during the drug product's life cycle.

[18] 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 as a general correspondence to the application, 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* (November 2020) and *Controlled Correspondence Related to Generic Drug Development* (December 2020).

VI. 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 SVP drug products for PN solutions in a subpopulation because of the risk of aluminum toxicity, the INDICATIONS AND USAGE section can include limitations of use.[19] 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 SVP drug products used in TPN must contain the following statement that should be included within a subsection entitled *Aluminum Toxicity* or with a similar heading:[20]

> 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.

In addition to the risk of aluminum toxicity in premature neonates (preterm newborns),[21] there is also a risk of aluminum toxicity from the use of SVP drug products in PN beyond the neonatal

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[19] 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.

[20] 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, and therefore ISMP recommends 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. FDA does not intend to object to the use of the term *mcg* instead of *µg* in this context.

[21] See section IV of the ICH guidance for industry *E11 (R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population* (April 2018). (The neonatal period for preterm newborn infants is defined as beginning at birth and ending at the expected date of delivery plus 27 days.)

period in preterm infants.[22] Therefore, FDA recommends that the *Aluminum Toxicity* subsection also describe the risks of aluminum toxicity in preterm infants. Furthermore, because tissue loading may occur with lower daily amounts of aluminum in addition to lower rates of administration, FDA recommends that this subsection also describe this risk from lower daily amounts of aluminum in SVP drug products used in TPN. For example, the following additional language can be added to this subsection:

> For similar reasons, preterm infants who receive greater than 4 to 5 mcg/kg/day of parenteral aluminum can accumulate aluminum at levels associated with aluminum toxicity (central nervous system and bone toxicity). Tissue loading may also occur in patients with renal impairment, including premature (preterm) neonates and preterm infants, from lower daily amounts of aluminum.

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 SVP drug products used in the preparation of TPN solutions with a total admixed aluminum content of no more than 5 mcg/kg/day, the following is an example of how to include such information in the *Aluminum Toxicity* subsection:

> Exposure to aluminum from DRUG-X at the recommended dosage is not more than Y[25] 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)]*.

If the total aluminum exposure is no more than 5 mcg/kg/day in a subpopulation (e.g., subpopulation-A) but exceeds 5 mcg/kg/day in another subpopulation (e.g., subpopulation-B), the drug product may be approved in subpopulation-A but in subpopulation-B, use is not recommended because of the risks of aluminum toxicity. The following is an example of how to include information in the *Aluminum Toxicity* subsection when SVP or PBP drug products are approved for use in the preparation of PN solutions in one subpopulation (e.g., patients 1 year of age and older) when the total aluminum exposure does not exceed 5 mcg/kg/day, but use is not recommended in another subpopulation (e.g., patients younger than 1 year of age) because of the

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[22] See the ICH guidance for industry *E11 (R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population*. Infants and toddler period is defined as 28 days to 23 months old.

[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] Y equals IAE_{SVP} and is determined from calculations described above in this guidance (see section IV.A., Determination of IAE_{SVP} of Drug Products with Known or Labeled Aluminum Concentration).

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 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 risks 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).[26] In this situation, the following is an example of aluminum toxicity information in this subsection:

> DRUG-X contains aluminum that may be associated with central nervous system and bone toxicity. Because of immature renal function, preterm infants receiving prolonged parenteral nutrition treatment with DRUG-X may be at higher risk of aluminum toxicity *[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.[27] In this situation, the following is an example of aluminum toxicity information in this subsection when the use of the drug product in pediatric patients is based on age:[28]

> 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 risks of aluminum toxicity *[see Warnings and Precautions (5.x)]*.

4. Description Section

For SVP drug products and PBPs used in the preparation of PN solutions, the DESCRIPTION section should contain a statement regarding the amount of aluminum in the drug product. The following is an example of this statement:

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[26] 21 CFR 201.57(c)(9)(iv)(B), (C), and (D).

[27] 21 CFR 201.57(c)(9)(iv)(E) or (F).

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

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

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

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

However, if the maximum level of aluminum in one of the lyophilized powder products 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

The maximum level of aluminum present at expiry must be stated on the immediate container label and carton labeling[29] of all SVP drug products used in the preparation of TPN solutions as follows:[30]

> Contains no more than X µg/L of aluminum.

However, if the maximum level of aluminum in one of these drug products 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:[31]

> Contains no more than 25 µg/L of aluminum.

If the SVP drug product is a lyophilized powder (*for injection* dosage form), the immediate container label and carton labeling must state the following:[32]

> When reconstituted in accordance with the package insert instructions, the concentration of aluminum will be no more than X µg/L.

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[29] 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."

[30] 21 CFR 201.323(c). In this statement, FDA does not intend to object to the use of the term *mcg* instead of *µg* in this context. See footnote #20.

[31] 21 CFR 201.323(d). In this statement FDA does not intend to object to the use of the term *mcg* instead of *µg* in this context. See footnote #20.

[32] 21 CFR 201.323(c). In this statement FDA does not intend to object to the use of the term *mcg* instead of *µg* in this context. See footnote #20.

However, if the 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:[33]

> 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 must be stated as the highest of one of the following:

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

2) The highest level for the latest five batches, or

3) The maximum historical level, but only until completion of production of the first five batches after July 26, 2004.[34]

[33] 21 CFR 201.323(d). In this statement FDA does not intend to object to the use of the term mcg instead of µg in this context. See footnote #20.

[34] 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 total parenteral nutrition (TPN) (SVP and LVP drug products) 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 TPN (SVP and LVP drug products) therapy; the value not to exceed is variable among individual drug products and is dependent on the component and composition of the TPN 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 (conc.) (milligram/milliliter (mg/mL)): The amount of the drug expressed in milligram per milliliter of the individual drug product defined in application.[1]

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., small volume parenteral (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 International Council for Harmonisation 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. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

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 drug product
$IAE_{LVPtotal}$	total aluminum exposure from large volume parenteral drug products
IAE_{SVP}	individual aluminum exposure from small volume parenteral drug product
$IAE_{SVPtotal}$	total aluminum exposure from small volume parenteral drug products
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
PPN	peripheral parenteral nutrition
QTPP	quality target product profile
RLD	reference listed drug
SVP	small volume parenteral
TAE	total aluminum exposure
TPN	total parenteral nutrition
USP	United States Pharmacopeia

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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* (December 2020)

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[1] We update guidances periodically. To make sure you have 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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