Table 10 *(Continued)*

Standard Solution	Concentration of Neu5Ac after Labeling (μM)	Concentration of Neu5Gc after Labeling (μM)
4	0.2	0.01
5	0.4	0.02

Sample solution: Transfer a desalted sample containing approximately 0.5–50 μg of protein (equivalent to about 5 pmol of sialic acid) into a 0.5-mL microcentrifuge tube. Dry in a vacuum centrifuge without heating. Add 25 μL of 2 M acetic acid into the tube and briefly centrifuge to ensure all of the sample is in the well of the tube. Incubate at 80° for 2 h ± 15 min. [NOTE—Or use validated sample preparation and time/temperature ranges.] Allow the tube to cool to room temperature for approximately 10 min. Then vortex and centrifuge. Label the solution as directed in *Labeling* before analysis.

• **USP REFERENCE STANDARDS ⟨11⟩**

USP *N*-Acetylneuraminic Acid RS

USP *N*-Glycolylneuraminic Acid RS

USP KDN RS

3-Deoxy-D-glycero-D-galacto-2-nonulosonic acid.

■1S (*USP40*)

⟨232⟩ ELEMENTAL IMPURITIES—LIMITS

Change to read:

INTRODUCTION

This chapter specifies limits for the amounts of elemental impurities in drug products. ■Regardless of the approach used, compliance with the limits specified is required for all drug products unless otherwise specified in an individual monograph or specifically excluded in this *Introduction*.■1S (*USP40*)

Elemental impurities include catalysts and environmental contaminants that may be present in drug substances, excipients, or drug products. These impurities may occur naturally, be added intentionally, or be introduced inadvertently (e.g., by interactions with processing equipment and the container–closure system). When elemental impurities are known to be present, have been added, or have the potential for introduction, assurance of compliance to the specified levels is required. A risk-based control strategy may be appropriate when analysts determine how to assure compliance with this standard. Due to the ubiquitous nature of arsenic, cadmium, lead, and mercury, they (at the minimum) must be considered in the risk assessment.

■This chapter does not apply to:

- Radiopharmaceuticals
- Articles intended only for veterinary use
- Vaccines
- Cell metabolites
- DNA products
- Allergenic extracts
- Cells, whole blood, cellular blood components, or blood derivatives, including plasma and plasma derivatives
- Products based on genes (gene therapy)
- Cells (cell therapy)
- Tissue (tissue engineering)
- Dialysate solutions not intended for systemic circulation
- Total parenteral nutritions (TPNs)
- Elements that are intentionally included in the drug product for therapeutic benefit
- Dietary supplements and their ingredients, which are addressed in *Elemental Contaminants in Dietary Supplements* ⟨2232⟩

■1S (*USP40*)

The limits presented in this chapter do not apply to excipients and drug substances, except where specified in an individual monograph. ■However, manufacturers of pharmaceutical products need certain information about the content of elemental impurities in drug substances or excipients in order to meet the criteria of this chapter. Drug product manufacturers can use elemental impurity test data on components from tests performed by drug substance or excipient manufacturers, who may provide test data, or if applicable, risk assessments. Elemental impurity data generated by a qualified supplier of drug product components are acceptable for use by a drug product manufacturer to demonstrate compliance with this chapter in the final drug product. Drug substance or excipient manufacturers who choose to perform a risk assessment must conduct that risk assessment using *Table 2* in this chapter. Elements that are inherent in the nature of the material, as in the case of some naturally-sourced materials, must be considered in the risk assessment.■1S (*USP40*)

SPECIATION

The determination of the oxidation state, organic complex, or combination is termed "speciation". Each of the elemental impurities has the potential to be present in differing oxidation or complexation states. However, arsenic and mercury are of particular concern because of the differing toxicities of their inorganic and complexed organic forms.

The arsenic limits are based on the inorganic (most toxic) form. Arsenic can be measured using a total-arsenic procedure under the assumption that all arsenic contained in the material under test is in the inorganic form. Where the limit is exceeded using a total-arsenic procedure, it may be possible to show, via a procedure that quantifies the different forms, that the inorganic form meets the specification.

The mercury limits are based upon the inorganic (2^+) oxidation state. The methyl mercury form (most toxic) is rarely an issue for pharmaceuticals. Thus, the limit was established assuming the most common (mercuric) inorganic form. Limits for articles that have the potential to contain methyl mercury (e.g., materials derived from fish) are to be provided in the monograph.

Change to read:

ROUTES OF EXPOSURE

■The elements included in the tables below have been placed into three classes, based on their toxicity and likelihood of occurrence in the drug product. The classification scheme is intended to focus the risk assessment on those elements that are the most toxic but also have a reasonable probability of inclusion in the drug product (see *Table 2*).■1S *(USP40)*

The toxicity of an elemental impurity is related to its extent of exposure (bioavailability). The extent of exposure has been determined for each of the elemental impurities of interest for three routes of administration: oral, parenteral, and inhalational. These limits are based on chronic exposure. Consider the oral permissible daily exposures (PDEs) in *Table 1* as a starting point in developing specific PDEs for other routes of administration, except where otherwise stated in the individual monograph.

[NOTE—The routes of administration of drug products are defined in *Pharmaceutical Dosage Forms* ⟨1151⟩.]

Change to read:

DRUG PRODUCTS

The limits described in the ■third■1S *(USP40)* through ■fifth■1S *(USP40)* columns of *Table 1* are the base daily dose PDEs of the elemental impurities of interest for a drug product taken by a patient according to indicated routes of administration.

Parenteral Products

Parenteral drug products with maximum daily volumes up to 2 L may use the maximum daily volume to calculate permissible concentrations from PDEs. For products whose daily volumes, as specified by labeling and/or established by clinical practice, may exceed 2 L (e.g., saline, dextrose, ■■1S *(USP40)* and solutions for irrigation), a 2-L volume may be used to calculate permissible concentrations from PDEs.

■

Table 1. Permitted Daily Exposures for Elemental Impurities

Element	Class	Oral PDE (μg/day)	Parenteral PDE (μg/day)	Inhalation PDE (μg/day)
Cadmium	1	5	2	2
Lead	1	5	5	5
Arsenic	1	15	15	2
Mercury	1	30	3	1
Cobalt	2A	50	5	3
Vanadium	2A	100	10	1
Nickel	2A	200	20	5
Thallium	2B	8	8	8
Gold	2B	100	100	1
Palladium	2B	100	10	1
Iridium	2B	100	10	1
Osmium	2B	100	10	1
Rhodium	2B	100	10	1
Ruthenium	2B	100	10	1
Selenium	2B	150	80	130

Table 1. Permitted Daily Exposures for Elemental Impurities *(Continued)*

Element	Class	Oral PDE (μg/day)	Parenteral PDE (μg/day)	Inhalation PDE (μg/day)
Silver	2B	150	10	7
Platinum	2B	100	10	1
Lithium	3	550	250	25
Antimony	3	1200	90	20
Barium	3	1400	700	300
Molybdenum	3	3000	1500	10
Copper	3	3000	300	30
Tin	3	6000	600	60
Chromium	3	11000	1100	3

Recommendations for Elements to be Considered in the Risk Assessment

Table 2 identifies elemental impurities for inclusion in the risk assessment. This table can be applied to all sources of elemental impurities in the drug product.

Table 2. Elements to be Considered in the Risk Assessment

Element	Class	If Intentionally Added (All Routes)	If Not Intentionally Added		
			Oral	Parenteral	Inhalation
Cadmium	1	Yes	Yes	Yes	Yes
Lead	1	Yes	Yes	Yes	Yes
Arsenic	1	Yes	Yes	Yes	Yes
Mercury	1	Yes	Yes	Yes	Yes
Cobalt	2A	Yes	Yes	Yes	Yes
Vanadium	2A	Yes	Yes	Yes	Yes
Nickel	2A	Yes	Yes	Yes	Yes
Thallium	2B	Yes	No	No	No
Gold	2B	Yes	No	No	No
Palladium	2B	Yes	No	No	No
Iridium	2B	Yes	No	No	No
Osmium	2B	Yes	No	No	No
Rhodium	2B	Yes	No	No	No
Ruthenium	2B	Yes	No	No	No
Selenium	2B	Yes	No	No	No
Silver	2B	Yes	No	No	No
Platinum	2B	Yes	No	No	No
Lithium	3	Yes	No	Yes	Yes
Antimony	3	Yes	No	Yes	Yes
Barium	3	Yes	No	No	Yes
Molybdenum	3	Yes	No	No	Yes
Copper	3	Yes	No	Yes	Yes
Tin	3	Yes	No	No	Yes
Chromium	3	Yes	No	No	Yes

■1S (*USP40*)

Options for Demonstrating Compliance

DRUG PRODUCT ANALYSIS OPTION

The results obtained from the analysis of a typical dosage unit, scaled to a maximum daily dose, are compared to the *Daily Dose PDE*.

Daily Dose PDE ≥ measured value (μg/g) × maximum daily dose (g/day)

The measured amount of each impurity is NMT the *Daily Dose PDE*, unless otherwise stated in the individual monograph.

SUMMATION OPTION

Separately, add the amounts of each elemental impurity (in μg/g) present in each of the components of the drug product:

$$\textit{Daily Dose PDE} \geq [\Sigma^{M}{}_{1}(C_M \times W_M)] \times D_D$$

M = each ingredient used to manufacture a dosage unit
C_M = element concentration in component (drug substance or excipient) (μg/g)
W_M = weight of component in a dosage unit (g/dosage unit)
D_D = number of units in the maximum daily dose (unit/day)

The result of the summation of each impurity is NMT the *Daily Dose PDE*, unless otherwise stated in the individual monograph. Before products can be evaluated using this option, the manufacturer must ensure that additional elemental impurities cannot be inadvertently added through the manufacturing process or via the container–closure system over the shelf life of the product.

INDIVIDUAL COMPONENT OPTION

For drug products with a daily dose of NMT 10 g, if all drug substances and excipients in a formulation meet the concentration limits shown in *Table 3*, then these components may be used in any proportion. No further calculation is necessary. While elemental impurities derived from the manufacturing process or the container–closure system are not specifically provided for in the *Individual Component Option*, it is expected that the drug product manufacturer will ensure that these sources do not contribute significantly to the total content of elemental impurities.

Change to read:

DRUG SUBSTANCE AND EXCIPIENTS

■The acceptable levels of elemental impurities depend on the material's ultimate use. Therefore, manufacturers of pharmaceutical products need certain information about the content of elemental impurities in drug substances or excipients in order to meet the criteria of this chapter. Drug product manufacturers can use elemental impurity test data on components from tests performed by drug substance manufacturers or excipient manufacturers, who may provide test data, or, if applicable, risk assessments. Elemental impurity data generated by a qualified supplier of drug product components are acceptable for use by a drug product manufacturer to demonstrate compliance with this chapter in the final drug product. Drug substance or excipient manufacturers who choose to perform a risk assessment must conduct that risk assessment using *Table 2* in this chapter. Elements that are inherent in the nature of the material, as in the case of some naturally-sourced materials, must be considered in the risk assessment.■1S *(USP40)*

The values provided in *Table 3* are example concentration limits for components (drug substances and excipients) of drug products dosed at a maximum daily dose of 10 g/day. These values serve as default concentration limits to aid discussions between drug product manufacturers and the suppliers of the components of their drug products. [NOTE—Individual components may need to be limited at levels different from those in the table depending on monograph-specific mitigating factors.]

■

Table 3. Permitted Concentrations of Elemental Impurities for Individual Component Option

Element	Class	Oral Concentration (μg/g)	Parenteral Concentration (μg/g)	Inhalation Concentration (μg/g)
Cadmium	1	0.5	0.2	0.2
Lead	1	0.5	0.5	0.5
Arsenic	1	1.5	1.5	0.2
Mercury	1	3	0.3	0.1
Cobalt	2A	5	0.5	0.3
Vanadium	2A	10	1	0.1
Nickel	2A	20	2	0.5
Thallium	2B	0.8	0.8	0.8
Gold	2B	10	10	0.1
Palladium	2B	10	1	0.1
Iridium	2B	10	1	0.1
Osmium	2B	10	1	0.1

Table 3. Permitted Concentrations of Elemental Impurities for Individual Component Option *(Continued)*

Element	Class	Oral Concentration (μg/g)	Parenteral Concentration (μg/g)	Inhalation Concentration (μg/g)
Rhodium	2B	10	1	0.1
Ruthenium	2B	10	1	0.1
Selenium	2B	15	8	13
Silver	2B	15	1	0.7
Platinum	2B	10	1	0.1
Lithium	3	55	25	2.5
Antimony	3	120	9	2
Barium	3	140	70	30
Molybdenum	3	300	150	1
Copper	3	300	30	3
Tin	3	600	60	6
Chromium	3	1100	110	0.3

■1S (*USP40*)

Change to read:

ANALYTICAL TESTING

If, by process monitoring and supply-chain control, manufacturers can demonstrate compliance, then further testing may not be needed. When testing is done to demonstrate compliance, proceed as directed in *Elemental Impurities—Procedures* ⟨233⟩. ■■1S (*USP40*)

OTHER TESTS AND ASSAYS

Delete the following:

■⟨371⟩ COBALAMIN RADIOTRACER ASSAY

All radioactive determinations required by this method should be made with a suitable counting assembly over a period of time optimal for the particular counting assembly used. All procedures should be performed in replicate to obtain the greatest accuracy.

USP REFERENCE STANDARD ⟨11⟩

USP Cyanocobalamin RS.

CYANOCOBALAMIN TRACER REAGENT

Dilute an accurately measured volume of a solution of radioactive cyanocobalamin* with water to yield a solution having a radioactivity between 500 and 5000 counts per minute per mL. Add 1 drop of cresol per L of solution prepared, and store in a refrigerator.

Standardization

Prepare a solution of a weighed quantity of USP Cyanocobalamin RS in water to contain 20 to 50 μg per mL. Perform the entire assay on a 10.0-mL portion of this solution, proceeding as directed under *Assay Preparation*, beginning with "Add water to make a measured volume."

* A solution of cyanocobalamin made radioactive by the incorporation of ^{60}Co is available from Merck and Co., Inc., Rahway, NJ 07065.