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December 20, 2013

Division of Dockets Management (HFA-305)
U.S. Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852
c/o Dr. John Kauffman
Re: Docket ID FDA-2013-D-1156

Dear Dr. Kauffman:

On behalf of the United States Pharmacopeial Convention (USP), I am pleased to submit to you the attached comments on the International Conference on Harmonisation Draft Guidance on Elemental Impurities (ICH Q3D Step 2b).

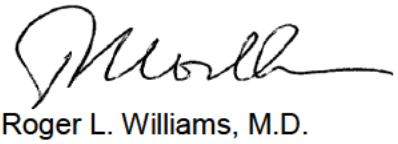
As you know, the USP Expert Panel and its antecedent groups, which were formed under the auspices of the General Chapters–Chemical Analysis Expert Committee and its antecedents, have been engaged in development of USP standards for elemental impurities for many years. We hope that these comments, which represent the thoughtful input of the Expert Panel's toxicologists and other scientists, will serve as an important contribution to FDA and to the Q3D Expert Working Group (EWG).

Independent of its work with the Q3D EWG, USP will soon propose revisions to official General Chapters <232> *Elemental Impurities–Limits* and <233> *Elemental Impurities–Procedures* with the expectation that the revisions will become official on August 1, 2015 in the *First Supplement to USP 38-NF 33*. Separate from these revisions, the USP Council of Experts has determined and will soon announce the official date for applicability of the General Chapters to drug product monographs. The Q3D EWG will appreciate that this date will represent a delay in the implementation of this important standard beyond the originally-proposed date of May 2014, recognizing that the existing standard (<231>) is of questionable utility.

In a recent meeting the week of December 16, 2013, USP and FDA attendees agreed that optimally no difference should exist between the list of elements tested and limits recommended by ICH and stated as official in the *USP-NF*. USP will make every effort to achieve this goal and would be pleased to meet with involved representatives of the ICH Q3D EWG at mutually convenient times. At the same time, USP believes it is important to finalize the standard as intended by the Expert Committee, with the understanding that further accommodations can be made over time via revisions to the *USP-NF*.

We thank the EWG for their contribution to standards for elemental impurities and look forward to continuing our support of the work of ICH Q3D through ongoing dialogue as feasible.

Sincerely yours,



Roger L. Williams, M.D.
Chie Executive Officer

cc: Dr. Paul Seo, Director of Compendial Operations, FDA

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USP Comments on ICH Q3D Step 2b Document of July 26, 2013

Mercury

On the basis of published assessments by the US Environmental Protection Agency and World Health Organization, USP maintains that a lower permitted daily exposure (PDE) of 15 mcg/day for inorganic mercury is justified. The ICH Q3D-derived oral PDE value of 40 mcg/day for mercury in the current step 2b document is only 3-fold higher than the long-standing US EPA reference dose (RfD) of 0.3 mcg/kg/day (or 15 mcg for a 50-kg person) and 3-fold higher than the WHO drinking water guideline value of 6 mcg/L (12 mcg, assuming water consumption of 2 L/day).

The current ICH Q3D derivation identifies the low dose from a 6-month gavage study in rats (NTP 1993) as a lowest-observed-adverse-effect level (LOAEL) for the point of departure. JECFA (2011) evaluated mercury as part of the "Safety evaluation of certain contaminants in food" and based the derivation of a 4 mcg/kg provisional tolerable weekly intake (PTWI) on the same 6-month gavage study. JECFA determined that the lowest $BMDL_{10}$ for increases in relative kidney weight in male rats corresponded to a mercury dose of 0.06 mg/kg bw per day. JECFA used the $BMDL_{10}$ as a point of departure and applied a 100-fold uncertainty factor. Using this $BMDL_{10}$ point of departure and applying the ICH Q3C modifying factors advocated in the step 2 document results in an oral PDE of 15 mcg/day that also aligns with the previously published guideline values:

Oral PDE = [0.06 mg/kg/day x 50 kg]/(5x10x2x1x2) = 15 mcg/day

The step 2 document explains the choice of F5 = 2 for "quality of data," but does not explain the choice of F4 = 1 for "nature of toxicity." Please consider further clarification of the uncertainty factors. In addition, consider that food is the main source of mercury exposure in non-occupationally exposed populations, and that a PDE of 40 mcg/day would be 2 to 20 times the mean dietary intake, which ranges from 2 to 20 mcg/day per person.

References:
World Health Organization. 2011. Guidelines for drinking-water quality. Fourth Edition. http://whqlibdoc.who.int/publications/2011/9789241548151_eng.pdf Accessed 09 December 2013.

World Health Organization (WHO)/Food and Agriculture Organization (FAO) Joint Expert Committee on Food Additives. WHO Food Additives Series: 63, FAO JECFA Monographs 8. Safety evaluation of certain contaminants in food. Prepared by the Seventy-second meeting of the Joint FAO/WHO Expert Committee of Food Additives (JECFA). 2011. http://www.inchem.org/documents/jecfa/jecmono/v63je01.pdf Accessed 09 December 2013.

Molybdenum

USP requests that ICH Q3D update the parenteral PDE for molybdenum to 90 mcg/day using a modifying factor of 2. The monograph for the parenteral PDE reads:

> In Vyskocil and Viau (1999), it was reported that oral bioavailability in humans ranged from 28-77%. Turnland et al (2005) report that molybdenum absorption was about 90% in healthy men. Therefore, the parenteral PDE is the same as the oral PDE.

However, Section 3.1 indicates that if oral bioavailability is <50%, then divide the oral PDE by a modifying factor of 10, and if oral bioavailability is between 50% and 90%, divide by a modifying factor of 2. Updating the parenteral PDE to 90 mcg/day would provide consistency with the principles outlined in Section 3.1.

Cadmium

USP proposes that ICH change the F5 cadmium uncertainty factor for quality of the data from 2 to 5 to account for dosing problems with the subcutaneous (SC) route of administration for this element. The SC route produces granulomas at the sites of injection over time that may trap an unspecified amount of the administered cadmium dose at the injection site. This phenomenon would decrease the actual parenteral cadmium dose, compared with the calculated parenteral cadmium dose, hence our request to increase the uncertainty factor. For this purpose, the use of data from intravenous (IV) cadmium dose studies would be preferable for calculations regarding the parenteral route.

Reference:
Waalkes MP, Anver M, Diwan BA. Carcinogenic effects of cadmium in the Noble (NBL/Cr) rat: induction of pituitary, testicular, and injection site tumors and intraepithelial proliferative lesions of the dorsolateral prostate. *Toxicol Sci*. 1999;52:154-161.

Platinum-Group Elements Palladium (Pd), Osmium (Os), Iridium (Ir), Ruthenium (Ru), and Rhodium (Rh)

USP does not regard the evidence as sufficient to justify considering the platinum assessment more relevant to the platinum-group metals than the palladium assessment. No data were provided supporting the ICH expert group's judgment to consider the toxicity of Os, Ru, Rh, and Ir to be similar to Pt but not to Pd. The only justification given was that there are no relevant data for Os, Ru, Rh, or Ir. USP does not consider it appropriate to extrapolate from chemical reactivity to biological effects without supporting data. Even the statement in the *Platinum* monograph (p. 56, *Introduction* line 4), "Platinum and Pd are more chemically reactive than the other platinoids," is questionable in this respect. Ru, Rh, and Ir may be more similar to platinum than to palladium with respect to chemical reactivity; however, this is not the case for osmium, which oxidizes in air even at room temperatures.

Furthermore, on the basis of a search for toxicity data for these elements and their compounds, the existing toxicological data (scarce as they are) clearly indicate that the toxicity of at least Os is much more similar to the toxicity of Pd than to that of Pt, and Os may also be chemically more similar to Pd. Rh data may point to a weak carcinogenic potential of rhodium chloride when ingested orally. Ir data are even more vague; it is known that the highly toxic oxide is only formed at high temperatures. For Ru, no data are available, but RuO_4 formed at high temperatures is considered to be highly toxic. Thus for Ir and Ru, given that the data are too weak or simply nonexistent, we are of the opinion that the limits should be oriented to the more-toxic Pd until sufficient data are available.

We recommend that the ICH expert group reconsider the evidence and further justify why the proposed limits for Os, Ru, Rh, and Ir have been set according to platinum. In the interests of safety, we believe that the palladium assessment should be used for Os, Ru, Rh, and Ir, as there is no conclusive evidence that these metals are more similar to platinum than to palladium with regard to toxicity.

Summarized Data for the Four Metals Os, Ir, Ru, and Rh

Os is more sensitive to oxidation than is Pd, and is much more sensitive than Pt. Os forms OsO_4 in contact with oxygen, even at room temperatures. OsO_4 has a high acute

toxicity and causes severe toxic effects in humans through inhalation, skin contact, or ingestion [1].

Ir is considered to be relatively inert to water, air, or acids, in contrast to Os or Pd. However, little information is available about health effects. A case study described a male worker who developed respiratory tract symptoms and contact urticaria when exposed to iridium chloride at work [2].

Rh is similarly inert to water, air, or acids. Common Rh salts were found to be less toxic than platinum salts in *in vitro* systems (neutral red reuptake test) [3]. A lifetime carcinogenicity bioassay in mice with rhodium chloride, however, was described to show a higher incidence of tumors in treated animals compared to controls at a dose of 5 ppm in drinking water [4], which is roughly equivalent to 200 ng/kg/d of rhodium chloride for a 25-g mouse.

Ru oxidizes in air at high temperatures to RuO_4, which is considered to be highly toxic, like OsO_4. Ingested ruthenium compounds are believed to be strongly retained in bones, and $RuCl_3$ is a strong irritant and corrosive. There are no toxicity excerpts for ruthenium, but it may be considered similar to platinum, and RuO_4 may have toxicity similar to OsO_4.

References:
The National Academies Press. In: *Prudent practices in the laboratory: handling and disposal of chemicals.* 1995. http://www.nap.edu/openbook/0309052297/html/167.html Accessed 09 December 2013.

Bergman A, Svedberg U, Nilsson E. Contact urticaria with anaphylactic reactions caused by occupational exposure to iridium salt. *Contact Dermatitis* 1995;32(1):14-17.

Bünger J, Stork J, Stalder K. Cyto- and genotoxic effects of coordination complexes of platinum, palladium and rhodium in vitro. *Int Arch Occup Environ Health* 1996;69(1):33-38.

Bingham E, Cohrssen B, Powell CH. In: *Patty's Toxicology.* Volumes 1-9. Fifth ed. New York, NY: John Wiley & Sons. 2001. p. V3 268.

Large-Volume Parenterals

The USP Elemental Impurities Expert Panel suggests that the ICH adopt the approach for analysis of large-volume parenteral (LVP) solutions that is specified in USP General Chapter <232> *Elemental Impurities–Limits*. The current ICH Q3D step 2b document (section 3.4 Parenteral Products) states that the parenteral PDEs are applied irrespective of dose volume. This can lead to impractically low component limits as the dose volume increases to 100 mL or more, which may be analytically impossible or, at best, extremely difficult to achieve. The USP approach expressly states the required limits for LVP solutions greater than 100 mL (which are readily obtainable in the laboratory and reflect the short-term exposure), and these are typical for most instances of LVP administration.

Topical and Mucosal Products

The proposed USP standard for topicals related to dermal and mucosal products is based upon the vetted US EPA *oral* RfDs for these major elemental impurities. This is thought to be more appropriate than the proposed ICH standards, which are based on parenteral IV dosing studies, because: 1) the USP standard is based on peer-reviewed ,and accepted data, which confers transparency, and 2) the oral route would take into account the metabolic conversions (e.g., methylation/demethylation reactions) made by the entire microbiome (GI flora) on the contaminants; these conversions may increase or decrease their toxic potential. The use of IV dosing, while more direct to the blood stream, does

not account for an unspecified fraction of the contaminant that would go into the liver and be transferred to the GI tract via biliary secretion. This fraction would also be acted upon by the microbiome to an unknown degree. The USP-proposed oral dosing route should therefore be more inclusive, transparent, and accurate with respect to the total biologically available dose.

Reference:
Claytona TA, Bakerb D, Lindona JC, Everett JR, Nicholson JK. Pharmacometabonomic identification of a significant host-microbiome metabolic interaction affecting human drug metabolism**.** *Proc Natl Acad Sci* 2009;106(34):14728-14733.

Rounding PDEs to Simplify Analytical Calibration Preparation

USP suggests rounding the PDEs down to the nearest number ending in 5 or 0 per the examples in Table 1 below. This would have minimal impact on the toxicological assessment (it would actually provide a small, additional safety factor) and would assist the analytical chemist in preparing multi-element calibration solutions from commercial stocks. These stocks tend to be pre-prepared in concentrations of 100, 1000, or 10,000 ppm.

Table 1. Permitted Daily Exposures for Elemental Impurities: Suggested Rounding to Simplify Analytical Procedures

Element	Class	Oral PDE, µg/day	Parenteral PDE, µg/day	Inhalation PDE, µg/day
As	1	15	15	1.5
Cd	1	5.0	6.0	3.0
Hg	1	40	4.0	1.0
Pb	1	5.0	5.0	5.0
Co	2A	50	5.0	2.5
Mo	2A	150	150	7.5
Se	2A	150	85	100
V	2A	100	10	1.0
Ag	2B	15	35	5
Au	2B	100	100	1.0
Ir3	2B	1000	10	1.0
Os3	2B	1000	10	1.0
Pd	2B	100	10	1.0
Pt	2B	1000	10	1.0
Rh3	2B	1000	10	1.0
Ru3	2B	1000	10	1.0
Tl	2B	5	5	65
Ba	3	13000	1300	300
Cr	3	11000	1100	2.5
Cu	3	1000	100	10
Li	3	750	350	25
Ni	3	600	60	6.0
Sb	3	1200	600	20
Sn	3	6000	600	60

Table 2. PDEs as Currently Published in Q3D

Element	Class	Oral PDE, µg/day	Parenteral PDE, µg/day	Inhalation PDE, µg/day
As	1	15	15	1.9
Cd	1	5.0	6.0	3.4
Hg	1	40	4.0	1.2
Pb	1	5.0	5.0	5.0
Co	2A	50	5.0	2.9
Mo	2A	180	180	7.6
Se	2A	170	85	140
V	2A	120	12	1.2
Ag	2B	170	35	6.9
Au	2B	130	130	1.3
Ir3	2B	1000	10	1.4
Os3	2B	1000	10	1.4
Pd	2B	100	10	1.0
Pt	2B	1000	10	1.4
Rh3	2B	1000	10	1.4
Ru3	2B	1000	10	1.4
Tl	2B	8.0	8.0	69
Ba	3	13000	1300	340
Cr	3	11000	1100	2.9
Cu	3	1300	130	13
Li	3	780	390	25
Ni	3	600	60	6.0
Sb	3	1200	600	22
Sn	3	6400	640	64