Elemental Impurities in Pharmaceutical Excipients

GANG LI,[1] DAVE SCHONEKER,[2,5] KATHERINE L. ULMAN,[5,3] JASON J. STURM,[4] LISA M. THACKERY,[4] JOHN F. KAUFFMAN[1]

[1]U.S. Food and Drug Administration, Division of Pharmaceutical Analysis, St. Louis, Missouri 63110
[2]Colorcon Inc., Harleysville, Pennsylvania 19438
[3]Dow Corning Healthcare Business, Midland, Michigan 48686-0994
[4]Dow Corning Analytical Sciences, Midland, Michigan 48686-0994
[5]IPEC-Americas, Arlington, Virginia 22201

Received 14 May 2015; revised 26 August 2015; accepted 28 August 2015

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.24650

ABSTRACT: Control of elemental impurities in pharmaceutical materials is currently undergoing a transition from control based on concentrations in components of drug products to control based on permitted daily exposures in drug products. Within the pharmaceutical community, there is uncertainty regarding the impact of these changes on manufactures of drug products. This uncertainty is fueled in part by a lack of publically available information on elemental impurity levels in common pharmaceutical excipients. This paper summarizes a recent survey of elemental impurity levels in common pharmaceutical excipients as well as some drug substances. A widely applicable analytical procedure was developed and was shown to be suitable for analysis of elements that are subject to United States Pharmacopoeia Chapter <232> and International Conference on Harmonization's Q3D Guideline on Elemental Impurities. The procedure utilizes microwave-assisted digestion of pharmaceutical materials and inductively coupled plasma mass spectrometry for quantitative analysis of these elements. The procedure was applied to 190 samples from 31 different excipients and 15 samples from eight drug substances provided through the International Pharmaceutical Excipient Council of the Americas. The results of the survey indicate that, for the materials included in the study, relatively low levels of elemental impurities are present. © 2015 The Authors. *Journal of Pharmaceutical Sciences* published by Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci

Keywords: trace elements; US FDA; trace metal; excipients; microwave-assisted digestion; ICP-MS; Analytical Chemistry; Global Health; Mass Spectrometry; Regulatory Science

INTRODUCTION

Procedures for controlling elemental impurities in pharmaceutical products are undergoing significant revision. Elemental impurity levels in pharmaceutical materials are currently controlled through concentration specifications for metal catalysts and reagents in drug substances and/or concentration-based compendial acceptance criteria for select elements or classes of elements in drug substances and excipients. For some materials, pharmaceutical manufacturers currently demonstrate that they meet the compendial limits on drug substances and excipients by applying pharmacopeial heavy metals tests based on sulfide precipitation such as the procedure described in the United States Pharmacopeia (USP) General Chapter <231> Heavy Metals.[1] These acceptance criteria are being replaced by element specific permitted daily exposures (PDEs) from finished drug products that are based on current toxicological assessments of the elements. The PDE concept was firmly established in the International Conference on Harmonization (ICH) Q3C guideline on residual solvents. These major changes in the control of elemental impurities in pharmaceutical products are the culmination of many years of discussion and planning.

In 1995, the USP published a stimuli article in Pharmacopeial Forum describing several problems with the sulfide precipitation method including poor, variable recoveries, lack of selectivity, loss of volatile elements, and questionable validity.[2] The article recommended the use of spiked control samples during validation and substitution of atomic absorption and other instrumental methods for USP <231>. In 1998, the European Medicines Agency (EMA) began to develop a guideline on residual catalysts in pharmaceuticals with the goal of establishing limits based on toxicological safety assessments of common catalytic elements.[3] In 2008, the EMA Guideline on Specification Limits for Residues of Metal Catalysts or Metal Reagents was officially implemented for new drug products. The EMA guideline introduced mass-based PDEs to establish permissible exposures in drug products rather than concentration limits in drug substances. The PDEs in the EMA guideline were based on assessments of toxicological data on individual metals.

Between 2000 and 2008, the USP initiated a series of workshops and stakeholder forums for the purpose of revising General Chapter <231> Heavy Metals. During this time, several papers evaluated the suitability of modern instrumental methods of analysis for elemental impurities in pharmaceutical articles and products.[4–6] In 2008, the USP commissioned the United States Institute of Medicine to organize a workshop to evaluate current elemental toxicology and capabilities of modern methods of elemental analysis. Later in 2008, the USP

Correspondence to: John Kauffman (Telephone: +314-539-2168; Fax: +314-539-2113; E-mail: John.Kauffman@fda.hhs.gov)
Gang Li's present address is Pall Corporation, 25 Harbor Park Dr., Port Washington, New York 11050-4664.

This article contains supplementary material available from the authors upon request or via the Internet at http://onlinelibrary.wiley.com.

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Journal of Pharmaceutical Sciences
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proposed to replace <231> with two chapters: <232>, which would establish safety based limits on elemental impurities in pharmaceutical products, and <233> which would establish appropriate criteria for methods for elemental analysis.[7] After several years of revision with input from a broad group of stakeholders, these chapters were finalized, and became official in February of 2013.

In 2009, the ICH initiated the Q3D expert working group on elemental impurities in pharmaceutical products with the intention of harmonizing technical requirements for elemental impurities in pharmaceutical products across three regions: Europe, Japan, and the US.[8] As with the EMA guideline and the USP chapters, the Q3D expert working group endeavored to set maximum PDEs for elemental impurities in pharmaceutical products based on an assessment of existing toxicological data for the oral, parenteral and inhalation routes of administration. Q3D reached Step 2 of the ICH process in June, 2013 and the guideline was published for public review and comment. Q3D reached step 4 in November of 2014, and the USP Expert Panel on Elemental Impurities aligned General Chapters <232> and <233> with Q3D to the extent possible.

A PDE is the total daily mass of an impurity which is considered safe on the basis of direct toxicity. This is now a well-established approach which limits the amount of an impurity that is ingested by the patient rather than setting concentration limits on pharmaceutical materials. However, when applied to elemental impurities in drug products, the PDE approach poses some challenges for users and suppliers of drug substances and excipients because measurable acceptance criteria are no longer imposed on individual components of the drug product. Rather, the drug product manufacturer must determine what concentrations of elemental impurities are permissible for a drug product on the basis of the mass of a maximum daily dose of the drug product and the element-specific PDEs. Elemental impurity levels in drug products may also be controlled by setting appropriate concentration limits on all components of a drug product, based on the mass of each component of the drug product.

Manufacturers and suppliers of drug substances and excipients are understandably concerned about the impact of the new standards and guidelines on the requirements for elemental impurities in their products. At present, when applicable, ingredient manufacturers demonstrate that their products comply with compendial concentration limits for elemental impurities. There is concern that pharmaceutical manufacturers may now request extensive quantitative assessment of all elemental impurities in the components of drug products to demonstrate that the drug products comply with the new standards and meet the recommendations of new guidances. Currently there is a dearth of publically available data on elemental impurity levels in most pharmaceutical ingredients, which imposes additional uncertainty on the impact of these new standards and guidances.

The purpose of this paper is to present a survey of elemental impurity concentrations in a variety of excipients commonly used in pharmaceutical products as well as some drug substances. The samples for this survey were provided by the members of International Pharmaceutical Excipient Council-Americas (IPEC-Americas), and were analyzed at the United States Food and Drug Administration (US FDA) Division of Pharmaceutical Analysis. The analysis of these materials utilized a robust method of closed vessel digestion which is suitable for a wide variety of excipients and drug substances with appropriate modification, and the digested samples were analyzed by inductively coupled plasma mass spectrometry (ICP-MS). The experimental section of this paper describes the details of the analytical procedure. This is followed by the analytical results and a description of the capabilities of the procedures. The paper concludes with a brief discussion of some analytical challenges, and some potential solutions to those challenges.

EXPERIMENTAL

Reagents and Materials

Concentrated nitric acid (70%), concentrated hydrochloric acid (37%), hydrogen peroxide (30%), and hydrofluoric acid (49%) were purchased from Fisher Scientific (Fair Lawn, New Jersey). All of these regents were trace metal grade. Diluted nitric acid and hydrochloric acid were used for analytical solutions and sample dilutions. 18 MΩ-cm deionized water was produced through a Milli-Q water purification system (Millipore, Bedford, Massachusetts). Multi-element standards and individual standards were purchased from High-Purity Standards (Charleston, South Carolina). Instrument tuning solution and pulse/analog (P/A) tuning solution were purchased from Agilent Technologies (Newport, Delaware). Metal-free polpropylene centrifuge tubes 15 mL and 50 mL were purchased from VWR (Radnor, Pennsylvania).

One hundred and ninety pharmaceutical excipient samples and 15 drug substance samples were supplied by excipient manufacturers through IPEC-Americas. The samples included 31 different excipients that are commonly used in pharmaceutical manufacturing and eight different drug substances, and many were provided from multiple manufacturers and in several lots from the same manufacturer. The samples were coded by IPEC-Americas' counsel before being shipped to the US FDA Division of Pharmaceutical Analysis such that the analysts were informed of the name of each material, but were blind to their precise lot number and origin, which were only known to counsel. Different manufacturers were denoted with letters, and different lots were denoted with numbers to convey information on material variability without disclosing the specific products under test.

Instrumentation

All quantitative analyses were performed with an Agilent 7700x quadruple ICP-MS system and a model ASX-500 Autosampler (Agilent Technologies). Standard, sample, and quality control solutions were delivered to the nebulizer via a peristaltic pump at 0.1 mL per minute, and the nebulizer converted the sample solution to a spray mist using gas (Ar). For most samples in this study, a glass nebulizer was used, but when hydrogen fluoride was included in the digestion cocktail a perfluoroalkoxyalkane nebulizer was used. The peristaltic pump also continuously delivered a multi-element solution containing lithium-6, scandium, yttrium, indium, terbium, holmium, lutetium, and bismuth to the nebulizer. These elements, delivered at a fixed composition relative to the sample flow rate, were used as internal standards to compensate for matrix effects and instrumental instabilities during analysis. Internal standards were selected for each elemental analyte such that their first ionization energies were similar and interferences were minimized.

 DOI 10.1002/jps.24650

Table 1. ICP–MS Instrumental Operational Conditions and Data Acquisition Parameters

	Standard Mode	Collision Gas Mode
RF power (W)	1550	1550
Plasma gas flow rate (L min^{-1})	14.97	14.97
Dilution gas flow rate (L min^{-1})	0.55	0.55
Nebulizer gas flow rate (L min^{-1})	0.6	0.6
Collision gas flow rate (mL min^{-1})	n.a.	4.5 (He) or 6.0 (High He)
Nebulizer	MicroMist (Borosilicate glass, id 0.5 mm)	MicroMist (Borosilicate glass, id 0.5 mm)
Spray chamber	Quartz, Scott-type	Quartz, Scott-type
Torch	Quartz, id 2.5 mm	Quartz, id 2.5 mm
Sampler and skimmer cones	Nickel	Nickel
Lens voltage (V)	7.6	7.6
Scan mode	Peak hopping	Peak hopping
Detector	Electron multiplier detector	Electron multiplier detector
Dwell time (s)	0.1	0.1
Sweeps	100	100
Readings/replicates	3	3

Table 2. Concentration Range of ICP–MS Calibration and Limit of Detection

Q3D Class	Element	Isotope	Standard Concentration Range (ng g^{-1})	Limit of Detection (LOD) (ng g^{-1})
1	Cd	111	0.5–50	0.038
	Pb	208	0.5–50	0.058
	As	75	0.5–50	0.050
	Hg	202	0.01–1.0	0.040
2A	Co*	59	0.5–50	0.042
	V	51	0.5–50	0.194
	Ni	60	0.5–50	0.074
2B	Tl*	205	0.5–50	0.086
	Au*	197	0.01–1.0	0.019
	Pd	105	0.02–2.0	0.152
	Ir	193	0.01–1.0	0.003
	Os	189	0.01–1.0	0.134
	Rh	103	0.01–1.0	0.002
	Ru	101	0.01–1.0	0.002
	Se*	78	0.5–50	0.652
	Ag*	107	0.5–50	0.005
	Pt	195	0.01–1.0	0.003
3	Li*	7	0.5–50	0.187
	Sb*	121	0.5–50	0.099
	Ba*	137	0.5–50	0.362
	Mo	95	0.5–50	0.237
	Cu	63	0.5–50	0.804
	Sn*	118	0.5–50	0.162
	Cr	52	0.5–50	0.051

Asterisks denote elements that are included in ICH Q3D, but not in USP <232>.

The instrument is equipped with an octopole collision cell utilizing 99.999% purity helium gas to deflect molecular interferents from the ion path as discussed below. Instrumental settings were optimized daily prior to analysis using a tuning solution containing Li, Co, Ce, Tl, and Y to establish system suitability. Automated adjustments to the torch alignment, detector voltage, and ion lens voltages optimized resolution, sensitivity, and stability across a broad range of masses. The doubly charged ion ratio (Ce^{2+} to Ce^{+}), and oxide ratio (CeO^{+} to Ce^{+}) were also monitored, and were maintained below 5% and 2%, respectively. Three collision gas conditions were used: no gas, helium gas, and high helium gas, as described below. The isotopic masses under investigation were scanned under one or more collision gas conditions with an equilibration time of 30 s between conditions to pressurize or evacuate the collision cell. Typical instrumental and operating conditions are given in Table 1, and a typical, automated measurement of a single sample for all elements under all conditions described above required approximately 5 min.

Samples were prepared by closed vessel acid digestion using a Milestone Ethos Series SK-10 microwave digestion system with segmented rotor vessels (Milestone Inc., Shelton, Connecticut). The microwave digestion system is equipped with temperature and pressure sensors. In some cases, the pressure sensor was used for digestion method development, but the method parameters are based on temperature control and so pressure was not routinely controlled during sample digestion. The Teflon vessels have a volume of 100 mL, a maximum pressure of 100 bar and a maximum temperature of 300°C. This system features a "vent-and-reseal" design that prevents overpressure without losing samples. A typical time-temperature digestion cycle was to ramp to 190°C over 10 min, hold at 190°C for 20 min, and cool to room temperature. With this system, 10 samples can be digested simultaneously.

Standard Preparation

Four standard concentrations plus a blank solution were used to prepare calibration curves for each element. The calibration standards were prepared by diluting the 10 mg L^{-1} stock standards of single-element and multi-element standards with 2% (*v*/*v*) HNO_3 and 0.5% (*v*/*v*) HCl. For most elements, the standard concentrations ranged from 0 to 50 ng per gram of solution (ppb). Concentrations for the platinum group elements, gold, and mercury ranged from 0 to 1 ppb to reduce the potential for memory effects and element carry over. The isotopes used for analysis and the calibration concentration ranges of the standards are reported in Table 2. Quality control and calibration verification samples containing all elements under study, including the continuing calibration blank (CCB), low-level continuing calibration verification (LLCCV) standard, and continuing calibration verification (CCV) standard were also prepared separately from stock solutions. The calibration blank and CCB were prepared separately from the sample matrix (usually 2% HNO_3 and 0.5% HCl) but served different analytical purposes. The calibration blank was used as a calibration standard with zero analyte concentration, whereas the CCB was used to periodically verify the absence of carryover from one sample to the next. The LLCCV concentration was approximately equal to the second lowest non-blank standard, and the CCV concentration was approximately the midpoint of the calibration standard range. These control and calibration samples were measured throughout each analysis run, typically every five samples, as described below, to continually verify the accuracy of the measurements.

Sample Preparation

Samples were prepared for analysis by closed-vessel microwave-assisted digestion as described above. All relevant solution parameters (sample mass, tube mass, diluent added) were measured gravimetrically at a precision of ±0.1 mg. A typical digestion solution comprised 2 mL of concentrated HNO_3 and 2 mL of concentrated HCl. For some organic materials, 30% hydrogen peroxide (~1 mL) was added to enhance oxidative degradation processes. In some cases, 0.7 mL HF (50%) was added to digest materials that could not be digested completely with HNO_3 and HCl (e.g., talc, TiO_2, SiO_2). Decisions about the addition of HF and hydrogen peroxide were made on the basis of material knowledge and visual examination of the diluted samples. When solid was observed in the diluted sample, adjustments were made to the digestion cocktail (e.g., addition of H_2O_2 and HF) to minimize the solid, and samples digested with and without the additives were run to establish recoveries under both conditions. Typically, 0.2–0.3 g of an excipient was digested in about 3 mL of an acid cocktail at ~190°C in Teflon vessels. The vessels were brought to temperature over a period of 10 min, and temperature was maintained for 20 more minutes before allowing the vessels to cool to room temperature over the course of approximately 30 min. The cooled samples were then delivered to 50 mL trace metal free polypropylene tubes (VWR) and diluted with 18.2 MΩ-cm DI water to a volume of about 30 mL (diluent measured gravimetrically) for a total dilution factor of about 100 with respect to the original sample mass. This resulted in a solution composition of about 2% (*v*/*v*) HNO_3 and 0.5% (*v*/*v*) HCl, accounting for estimated loss due to NO_x formation and HCl evaporation.

Sample Analysis

Digested and diluted samples were prepared and analyzed in 23 separate ICP-MS runs over a span of about 9 months. After tuning the instrument and determining system suitability, the samples were analyzed for all elementals shown in Table 2. A typical measurement sequence was programmed as follows. Calibration standards were run at the beginning of the sequence including a matrix blank, a calibration blank, calibration standards, CCB, LLCCV, CCV, and another calibration blank. The calibration standards were used to establish a linear calibration curve for each element. After the initial measurement of calibration and quality control standards, the remainder of the sequence included the following: (1) measurement of five samples, (2) measurement of CCB, LLCCV, calibration blank, CCV, and another calibration blank. Parts (1) and (2) were repeated sequentially until all samples in the measurement run were completed. LLCCV and CCV served as quality control standards to assess the recoveries of each element in each run. If the recovered concentrations did not agree to within ±20% of the theoretical concentrations for all continuing calibration validation solutions during the analysis, further investigation of the results was conducted and, when necessary, repeated. Results from approximately 10 samples were based on repeated measurements performed in the last three measurement groups. Details regarding measurement groups can be found in the Supporting Material. Quality control standards also provided a measure of the variance associated with the analysis of samples.

In each run, 24 elements including Cd, Pb, As, Hg, Co, V, Ni, Tl, Au, Pd, Ir, Os, Rh, Ru, Se, Ag, Pt, Li, Sb, Ba, Mo, Cu, Sn, and Cr were measured, some at multiple isotopic masses to identify and correct for interferences. A collision cell containing helium was used during analysis of some elements with common polyatomic interferences to reduce the interfering ion concentrations. V, Cr, Co, Ni, Cu, and Mo were determined in He mode with a He flow rate of 4.5 mL min^{-1}, and As-75 and Se-78 were monitored in high He mode with a helium flow rate of 6.0 mL min^{-1}. The rest of the elements were analyzed with no gas in the collision cell.

Linear calibration curves were established using linear regression on the signal levels against the gravimetrically determined element concentrations for each element at each isotopic mass under study. The coefficient of determination (R^2) values for the signal response functions were generally greater than 0.999. Pb counts were corrected for geographical differences in isotopic distribution by calibration on the sum of Pb-206, Pb-207, and Pb-208 counts, except when samples contained large concentrations of bismuth. In this case, the bismuth signal may overlap with Pb-208, and the Pb-206 and Pb-207 signals were used to estimate Pb concentration. The isotopes Cd-106 and Cd-108 were also monitored for the correction of Cd-111 interferents.

RESULTS

Table 2 displays the isotopes used for analysis, calibration sample concentration ranges and solution limits of detection (LODs) for each element which is listed in the ICH Q3D guideline. The Q3D element classes, which are intended to assist the risk assessment of elemental impurities in drug products, are also identified, and elements that are listed in Q3D but are not covered by USP <232> are indicated with an asterisk. In each run, the instrumental LODs for each element were established as three times the SD of all blanks (CCBs and calibration blanks) measured in that run, and the LODs listed in Table 2 are averages of 23 ICP-MS runs performed over a period of approximately 9 months. The reported LODs are all less than 1 ppb, and the highest LOD is ~0.8 ppb for Cu, which is known to have several interferences. Selenium has a LOD of ~0.7 ppb owing to argon and chloride molecular ion interferences. Twenty (20) of the remaining 22 element LODs are below 0.2 ppb, and the ICH Q3D Class 1 elements (Cd, Pb, As, and Hg) have LODs below 0.06 ppb. Although chloride ion in the matrix is known to interfere with As and Se, the collision cell in high He mode substantially reduced these polyatomic interferences. When dilution factors of ~100 are used to dilute the original excipient samples, the resulting LODs in the pharmaceutical materials are expected to be in the range of 1–20 ppb for most elements. Assuming that limits of quantitation (LOQs) are 3.3 times the LODs, LOQs are expected to be in the range of 3–65 ppb for most elements. The Q3D Option 1 concentrations can be used to put these LOQs in context. The Option 1 concentrations are calculated by dividing the element specific PDEs by 10 g, and indicate concentrations that may be present in drug products with maximum daily doses of up to 10 g without exceeding the PDEs. The Q3D Option 1 concentrations range from 100 ppb to 1100 ppm. Thus the sensitivities characterized by the LOQs discussed above are adequate for quantitative analysis at all final ICH Q3D Option 1 concentrations by oral, parenteral and inhalation routes of administration.

 DOI 10.1002/jps.24650

Table 3. Summary of Quality Control Standards Performances

Element	Isotope	LLCCV Recovery	CCV Recovery
Cd	111	98% ± 4%	99% ± 3%
Pb	208	98% ± 8%	99% ± 8%
As	75	94% ± 12%	98% ± 10%
Hg	202	91% ± 16%	99% ± 8%
Co	59	98% ± 5%	100% ± 6%
V	51	101% ± 8%	101% ± 6%
Ni	60	97% ± 8%	100% ± 6%
Tl	205	97% ± 11%	99% ± 13%
Au	197	95% ± 10%	100% ± 6%
Pd	105	92% ± 24%	92% ± 22%
Ir	193	95% ± 8%	99% ± 4%
Os	189	89% ± 22%	98% ± 6%
Rh	103	93% ± 10%	100% ± 3%
Ru	101	93% ± 12%	95% ± 22%
Se	78	95% ± 9%	99% ± 10%
Ag	107	98% ± 4%	99% ± 3%
Pt	195	95% ± 8%	98% ± 6%
Li	7	97% ± 4%	99% ± 3%
Sb	121	97% ± 6%	100% ± 4%
Ba	137	100% ± 5%	101% ± 3%
Mo	95	98% ± 5%	100% ± 6%
Cu	63	92% ± 15%	96% ± 11%
Sn	118	96% ± 6%	99% ± 5%
Cr	52	99% ± 8%	100% ± 6%

The recoveries for the LLCCV and CCV quality control samples are displayed in Table 3. The analyses of these two standards were repeated every five samples within each run to monitor the stability of the system and assure continued quality of the measurements. The calculated concentration of each element in the LLCCV and CCV samples was compared with the theoretical concentration of the element in the gravimetrically prepared samples. Recovery values displayed in Table 3 are the means and SDs of CCV and LLCCV samples measured in 23 runs over a period of approximately 9 months. The mean recoveries were between 89% and 101%, with most being close to 100%. The LLCCVs display higher variability than the CCVs owing to the lower concentrations of these samples. Variability is typically highest in the elements with calibration standard ranges of 0.01–1 ppb (e.g., Hg and the Pt series) and elements with known interferences (e.g., Se, Cu, and As). Variability in Os and Pd may also result from facile formation of volatile oxides for these elements. The CCV recoveries display lower variability and confidence intervals between 83% and 105%. These results demonstrate satisfactory quality control of the measurement system.

The summary results of the analysis of 190 excipient samples and 15 drug substance samples are shown in Tables 4–7. The drug substances are displayed in the bottom 8 rows of the tables. The complete data set used to generate Tables 4–7 is available in the Supporting Material. The sample solution concentrations were predicted from signal levels using the linear regression calibration equations, and concentrations in the original materials were determined after multiplying the solution concentrations by the sample dilution factors to give concentrations in micrograms of the elemental impurity per gram of excipient (parts per million, ppm) to 2 decimal places. Samples with predicted concentrations lower than the LOD for a given element were labeled as <LOD. Elemental impurities with concentrations less than 0.005 ppm in the samples were rounded to a value of 0.00. SDs of 0.00 in Tables 4–7 indicate values less than 0.005. Elemental impurity concentrations in the excipients and drug substances without rounding are given in the Supporting Material.

When several samples of a specific excipient were available, the average elemental impurity concentrations and SDs were reported in Tables 4–7. Some of these samples were multiple lots from the same manufacturer, and some were sampled across manufacturers. This level of detail has not been provided in Tables 4–7, but the interested reader may assess the within-supplier and between-supplier variabilities in these concentrations by examining the data provided in the Supporting Material.

Table 4 displays the summary concentrations of Q3D Class 1 impurities in the pharmaceutical excipients and drug substances evaluated in this work. With the exception of some results for Pb, the measured ICH Q3D Class 1 elemental impurity concentrations shown in Table 4 were found to be extremely low in these materials. Levels of Cd and Hg were found to be less than 1 ppm in all excipients analyzed, and 10 ppb or less in drug substances. Titanium dioxide showed relatively high and variable Pb concentrations of 2.15 ± 1.81 ppm. Synthetic excipients and drug substances and cellulose-based materials had Class 1 levels either below the LODs or in the 1–10 ppb range. Some excipients with metal counter ions had Class 1 concentrations in the 100 ppb range, and excipients and drug substances expected to be sourced from mined raw materials also had Class 1 concentrations in the 100–900 ppb range. Four of the excipients exceed the ICH Q3D Option 1 oral concentrations for 1 or more elemental impurities: TiO_2 and Zn Stearate exceed the Q3D Option 1 concentration for Pb and MgOH and $CaCO_3$ exceed the Q3D Option 1 concentration for Cd.

Table 5 displays the summary concentrations for the Q3D Class 2B elements. All materials displayed very low concentrations of the ICH Q3D Class 2B elements including Ag, Au, Tl, and platinum group elements, and no excipients or drug substances exceeded the ICH Q3D Option 1 oral concentrations for Class 2B elements. Q3D Class 2B comprises precious metals and other elements that are unlikely to be present in drug products unless they are intentionally added. Most of the excipients were below the element LODs. Silicone elastomer and silicone tacky gel samples were exceptions, and were found to contain Pt concentrations of 3.75 ± 3.76 ppm and 6.39 ± 0.14 ppm, respectively. These samples use Pt-containing catalysts during polymer synthesis. Of the materials that had measureable levels of Class 2B elements, one (bismuth subsalicylate) had Ag at a level of 0.7 ppm and one (Zn Stearate) had Se at a level of 0.14 ppm. All others were less than 0.09 ppm. The results for the Class 2B elements are consistent with the expectation that these elements are rarely found in pharmaceutical materials unless they are intentionally added.

Table 6 shows the summary concentrations of the Q3D Class 2A elements, and demonstrates that the ICH Q3D Class 2A elements (Co, V, and Ni) were also found at low levels in most excipients and drug substances. Iron oxides showed relatively high concentrations (~100 ppm) of V, Ni, and Co, and the mean values of these concentrations exceeded the ICH Q3D Option 1 oral concentrations. Carbonyl iron samples also exhibited levels of Ni that exceeded the Option 1 oral concentrations. From these results, it appears that Class 2A elements may be commonly found in Fe containing excipients and drug substances.

Table 4. Class 1 Elemental Impurity Concentrations in Excipient Samples. Concentrations given as <LOD Indicate Levels Below the Method Limit of Detection

N (Number of Samples)	Materials Name	Cd (ppm)	Pb (ppm)	As (ppm)	Hg (ppm)
5	Ferric oxide red	<LOD	0.37 ± 0.21	0.66 ± 0.32	0.00 ± 0.00
5	Ferric oxide yellow	<LOD	0.28 ± 0.36	0.80 ± 0.41	0.00 ± 0.01
5	Ferrous oxide black	<LOD	0.03 ± 0.03	0.04 ± 0.01	<LOD
11	Talc	0.00 ± 0.00	0.19 ± 0.06	0.17 ± 0.05	0.01 ± 0.01
7	Titanium dioxide	0.04 ± 0.02	2.15 ± 1.81	0.08 ± 0.13	0.01 ± 0.02
3	Silicon dioxide	0.02 ± 0.01	0.12 ± 0.04	0.01 ± 0.00	0.01 ± 0.00
13	Calcium phosphates	0.03 ± 0.01	0.03 ± 0.01	0.24 ± 0.18	0.00 ± 0.00
5	Carrageenan	0.25 ± 0.22	0.15 ± 0.10	0.52 ± 0.18	0.01 ± 0.01
26	Calcium carbonate	0.77 ± 0.10	0.18 ± 0.59	0.04 ± 0.04	0.00 ± 0.01
17	Sodium alginate	0.01 ± 0.01	0.42 ± 0.30	0.42 ± 0.20	0.00 ± 0.00
9	Silicone elastomer	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.01	<LOD
9	Simethicone	0.00 ± 0.00	<LOD	<LOD	<LOD
9	Simethicone emulsion	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	<LOD
6	Dimethicone	<LOD	0.00 ± 0.00	<LOD	<LOD
3	Silicone tacky gel	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.01	<LOD
3	Polydimethysiloxane	0.00 ± 0.00	0.01 ± 0.02	0.00 ± 0.00	<LOD
17	Povidone	0.00 ± 0.00	0.00 ± 0.01	0.00 ± 0.01	<LOD
3	Ethylcellulose	<LOD	<LOD	0.00 ± 0.00	<LOD
11	Carboxymethylcellulose	0.00 ± 0.00	0.09 ± 0.27	0.00 ± 0.01	<LOD
8	Hydroxypropylcellulose	0.00 ± 0.00	0.00 ± 0.00	<LOD	<LOD
6	Hypromellose	0.00 ± 0.00	0.01 ± 0.00	<LOD	<LOD
1	Zinc stearate	0.31	1.05	<LOD	<LOD
1	Magnesium stearate NF/EP	0.00	0.01	0.02	<LOD
1	Magnesium hydroxide granular	0.84	0.33	0.55	<LOD
1	Magnesium carbonate	0.43	0.07	0.13	<LOD
1	Blue #1	0.00	0.03	0.01	0.03
1	Red #27 Al.Lake	0.00	0.21	0.16	<LOD
1	Imidurea	<LOD	<LOD	<LOD	0.02
1	N-Methyl-2-pyrrolidone	<LOD	<LOD	<LOD	<LOD
1	2,5-Dioxo-4-imidazolidinyl	<LOD	<LOD	0.00	0.04
3	Tetracaine HCl	<LOD	0.01 ± 0.01	<LOD	<LOD
3	Orphenadrine citrate	<LOD	<LOD	<LOD	<LOD
2	Procainamide HCl	0.01 ± 0.01	<LOD	<LOD	<LOD
3	Benzonatate	0.00 ± 0.00	0.00 ± 0.01	<LOD	<LOD
1	Flunixin meglumine	0.00	0.00	<LOD	<LOD
1	Bismuth subsalicylate	0.00	0.15	0.02	<LOD
1	Carbonyl iron	0.01	<LOD	0.04	0.01
1	Bemotrizinol	<LOD	<LOD	<LOD	<LOD

Concentrations given as 0.00 indicate levels below the stated precision but above the LOD. Uncertainties given as 0.00 are below the stated precision. The bottom 8 rows display results for some drug substances.

The Q3D Class 3 elements have relatively low toxicity by the oral route of administration, with oral PDE ranging from 550–11,000 μg/day. PDEs for parenteral and inhalation routes are lower than the oral PDEs. Table 7 displays summary concentrations of the Q3D Class 3 elements. Data in Table 7 identify several excipients with relatively high levels of ICH Q3D Class 3 elements when compared with the levels of Class 1 and 2 elemental impurities in these same materials. For example, Fe oxides show elevated levels of Cr, Mo, Sn, and/or Cu, $CaCO_3$ show elevated levels of Cr and Ba, and talc, carrageenans, alginates, and Zn stearate show elevated levels of Ba compared with concentrations of their Class 1 and 2 elements. However, none of these levels exceed the ICH Q3D Option 1 concentration limits for oral or parenteral products. Thus, the observed levels of elemental impurities in these excipients are low relative to the relevant safety thresholds in finished drug products. Drug substances examined in this survey have extremely low levels of the ICH Class 3 elements, with the exception of carbonyl iron, which exhibits low levels of Mo and Cr.

DISCUSSION

Perhaps the most remarkable feature of this data set taken as a whole is that elemental impurity concentrations in the excipients examined within this study are generally low, and for most excipients, often well below 1 microgram of impurity per gram of excipient. However, some excipients had higher concentrations of certain elemental impurities when compared with the average values observed across all excipients. For instance, relatively high concentrations of Pb in TiO_2 and Class 2A and Class 3 elemental impurities in iron oxides were discussed above, but these observations were not unexpected. It is also not surprising that calcium carbonate and other mined excipients showed elevated concentrations of selected elemental

Table 5. Class 2B Elemental Impurity Concentrations in Excipient Samples Concentrations given as <LOD Indicate Levels Below the Method Limit of Detection

N (Number of Samples)	Materials Name	Tl (ppm)	Au (ppm)	Pd (ppm)	Ir (ppm)	Os (ppm)	Rh (ppm)	Ru (ppm)	Se (ppm)	Ag (ppm)	Pt (ppm)
5	Ferric oxide red	<LOD	<LOD	<LOD	0.00 ± 0.00	0.01 ± 0.02	–	<LOD	<LOD	0.00 ± 0.00	0.00 ± 0.00
5	Ferric oxide yellow	<LOD	<LOD	<LOD	<LOD	0.00 ± 0.01	–	0.00 ± 0.00	<LOD	<LOD	0.00 ± 0.00
5	Ferrous oxide black	<LOD	<LOD	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.01	–	<LOD	<LOD	0.00 ± 0.00	<LOD
11	Talc	0.00 ± 0.00	<LOD	0.00 ± 0.00	<LOD	0.00 ± 0.00	<LOD	0.00 ± 0.00	0.01 ± 0.03	0.00 ± 0.00	0.00 ± 0.00
7	Titanium dioxide	0.01 ± 0.03	0.04 ± 0.03	0.02 ± 0.02	0.00 ± 0.00	<LOD	0.00 ± 0.00	0.00 ± 0.00	0.02 ± 0.05	0.06 ± 0.05	0.01 ± 0.01
3	Silicon dioxide	<LOD	<LOD	<LOD	0.00 ± 0.00	0.00 ± 0.00	<LOD	0.00 ± 0.00	0.01 ± 0.02	0.04 ± 0.01	0.00 ± 0.00
13	Calcium phosphates	0.00 ± 0.01	0.00 ± 0.00	0.05 ± 0.05	<LOD	0.01 ± 0.03	0.01 ± 0.01	0.00 ± 0.00	0.01 ± 0.02	0.00 ± 0.00	0.00 ± 0.00
5	Carrageenan	0.00 ± 0.00	<LOD	0.04 ± 0.01	<LOD	<LOD	–	<LOD	<LOD	0.01 ± 0.01	<LOD
26	Calcium carbonate	0.00 ± 0.00	<LOD	0.13 ± 0.03	0.00 ± 0.00	0.00 ± 0.00	–	0.00 ± 0.00	0.02 ± 0.04	0.01 ± 0.00	0.00 ± 0.00
17	Sodium alginate	0.00 ± 0.00	<LOD	0.01 ± 0.02	<LOD	0.00 ± 0.00	<LOD	0.00 ± 0.00	<LOD	0.00 ± 0.00	0.00 ± 0.00
9	Silicone elastomer	0.00 ± 0.00	<LOD	0.00 ± 0.00	<LOD	<LOD	<LOD	0.00 ± 0.00	<LOD	0.00 ± 0.00	3.75 ± 3.76
9	Simethicone	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
9	Simethicone emulsion	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0.00 ± 0.00	<LOD
6	Dimethicone	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0.00 ± 0.00	<LOD
3	Silicone tacky gel	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0.00 ± 0.00	6.39 ± 0.14
3	Polydimethysiloxane	<LOD	<LOD	<LOD	<LOD	<LOD	0.00 ± 0.00	0.00 ± 0.00	<LOD	0.00 ± 0.00	0.00 ± 0.00
17	Povidone	<LOD	<LOD	<LOD	<LOD	<LOD	0.00 ± 0.00	0.00 ± 0.00	<LOD	0.00 ± 0.00	0.00 ± 0.00
3	Ethylcellulose	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0.00 ± 0.00	<LOD	0.00 ± 0.00	<LOD
11	Carboxymethylcellulose	<LOD	<LOD	0.02 ± 0.01	0.00 ± 0.00	<LOD	<LOD	0.00 ± 0.00	<LOD	0.00 ± 0.00	0.00 ± 0.00
8	Hydroxypropylcellulose	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0.00 ± 0.00	<LOD
6	Hypromellose	<LOD	0.00 ± 0.00	<LOD	<LOD	<LOD	<LOD	0.00 ± 0.00	<LOD	0.00 ± 0.00	<LOD
1	Zinc stearate	0.04	0.00	0.01	<LOD	<LOD	0.00	0.01	0.14	0.08	<LOD
1	Magnesium stearate NF/EP	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
1	Magnesium hydroxide granular	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0.00	<LOD
1	Magnesium carbonate	<LOD	<LOD	0.06	<LOD	<LOD	<LOD	<LOD	<LOD	0.00	<LOD
1	Blue #1	<LOD	<LOD	0.01	<LOD	<LOD	<LOD	<LOD	<LOD	0.00	<LOD
1	Red #27 Al.Lake	<LOD	<LOD	0.02	<LOD	<LOD	<LOD	0.00	<LOD	<LOD	<LOD
1	Imidurea	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0.00	<LOD	<LOD	<LOD
1	N-Methyl-2-pyrrolidone	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
1	2,5-Dioxo-4-imidazolidinyl	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
3	Tetracaine HCl	<LOD	<LOD	<LOD	<LOD	<LOD	–	<LOD	<LOD	<LOD	<LOD
3	Orphenadrine citrate	<LOD	<LOD	<LOD	<LOD	<LOD	–	<LOD	<LOD	<LOD	<LOD
2	Procainamide HCl	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
3	Benzonatate	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0.00 ± 0.00
1	Flunixin meglumine	<LOD	<LOD	0.01	<LOD	<LOD	<LOD	<LOD	<LOD	0.00	<LOD
1	Bismuth subsalicylate	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0.62	<LOD
1	Carbonyl iron	<LOD	<LOD	0.01	<LOD	<LOD	<LOD	<LOD	<LOD	0.00	<LOD
1	Bemotrizinol	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD

Concentrations given as 0.00 indicate levels below the stated precision but above the LOD. Uncertainties given as 0.00 are below the stated precision. The bottom 8 rows display results for some drug substances.

DOI 10.1002/jps.24650

Table 6. Class 2A Elemental Impurity Concentrations in Excipient Samples Concentrations given as <LOD Indicate Levels Below the Method Limit of Detection

N (Number of Samples)	Materials Name	Co (ppm)	V (ppm)	Ni (ppm)
5	Ferric oxide red	38.6 ± 16.6	436 ± 48	96.0 ± 13.1
5	Ferric oxide yellow	37.8 ± 13.5	407 ± 20	57.7 ± 30.6
5	Ferrous oxide black	123.5 ± 50.9	43.9 ± 0.1	154.4 ± 31.9
11	Talc	3.31 ± 2.31	5.30 ± 2.81	12.9 ± 9.1
7	Titanium dioxide	0.01 ± 0.02	3.69 ± 1.89	0.19 ± 0.15
3	Silicon dioxide	0.02 ± 0.01	0.14 ± 0.02	1.95 ± 1.11
13	Calcium phosphates	0.06 ± 0.05	3.92 ± 3.22	1.50 ± 1.23
5	Carrageenan	0.10 ± 0.08	0.47 ± 0.12	0.23 ± 0.12
26	Calcium carbonate	0.16 ± 0.03	1.78 ± 0.32	2.85 ± 0.68
17	Sodium alginate	0.02 ± 0.03	0.17 ± 0.25	0.37 ± 0.20
9	Silicone elastomer	0.00 ± 0.00	0.00 ± 0.01	0.12 ± 0.06
9	Simethicone	0.01 ± 0.00	<LOD	0.28 ± 0.02
9	Simethicone emulsion	0.04 ± 0.01	0.01 ± 0.00	2.92 ± 0.66
6	Dimethicone	0.00 ± 0.00	<LOD	0.02 ± 0.04
3	Silicone tacky gel	0.00 ± 0.00	<LOD	0.00 ± 0.01
3	Polydimethysiloxane	0.00 ± 0.00	<LOD	0.01 ± 0.02
17	Povidone	0.01 ± 0.03	0.01 ± 0.01	0.02 ± 0.03
3	Ethylcellulose	0.00 ± 0.00	0.01 ± 0.01	7.11 ± 2.60
11	Carboxymethylcellulose	0.02 ± 0.02	0.00 ± 0.00	0.54 ± 0.53
8	Hydroxypropylcellulose	0.02 ± 0.03	0.00 ± 0.01	0.07 ± 0.04
6	Hypromellose	0.00 ± 0.00	0.00 ± 0.01	0.44 ± 0.21
1	Zinc stearate	<LOD	<LOD	0.66
1	Magnesium stearate NF/EP	0.00	<LOD	0.16
1	Magnesium hydroxide granular	0.06	1.43	2.49
1	Magnesium carbonate	0.01	0.32	0.73
1	Blue #1	0.01	0.26	1.58
1	Red #27 Al.Lake	0.02	1.21	0.84
1	Imidurea	<LOD	0.02	<LOD
1	N-Methyl-2-pyrrolidone	<LOD	<LOD	<LOD
1	2,5-Dioxo-4-imidazolidinyl	<LOD	0.03	<LOD
3	Tetracaine HCl	0.00 ± 0.00	<LOD	0.02 ± 0.00
3	Orphenadrine citrate	0.00 ± 0.00	<LOD	0.01 ± 0.02
2	Procainamide HCl	<LOD	<LOD	0.01 ± 0.01
3	Benzonatate	<LOD	<LOD	0.03 ± 0.05
1	Flunixin meglumine	<LOD	<LOD	0.18
1	Bismuth subsalicylate	<LOD	<LOD	0.00
1	Carbonyl iron	0.01	<LOD	36.7
1	Bemotrizinol	<LOD	<LOD	0.01

Concentrations given as 0.00 indicate levels below the stated precision but above the LOD. Uncertainties given as 0.00 are below the stated precision. The bottom 8 rows display results for some drug substances.

impurities relative to concentrations of these same elemental impurities in other excipients. Most importantly, in the majority of cases when the observed concentrations of elemental impurities from these excipients were compared with relevant limits for potentially harmful elemental concentrations, the excipient's elemental impurity levels were found to be well below concentrations of concern.

A second key finding of this work was that, unless intentionally added, Class 2B metals were not observed at significant concentrations in any materials tested. This finding further supports the ICH Q3D approach to Class 2B elemental impurities during assessment of the risk for inclusion of elemental impurities in drug products. The results of this survey substantiate that it is generally appropriate to only include the Class 2B elemental impurities in a risk assessment when they are intentionally added to a component of the drug product.

Of particular interest to pharmaceutical manufacturers are scenarios where the observed concentrations of elements in any excipients would result in drug products that would exceed the PDEs for elemental impurities. Although unlikely, based on the results of this survey, PDE limits for a given elemental impurity could be exceeded if the drug product delivered a large mass of one or more excipients with elevated concentrations of elemental impurities to the patient. Based on comparison of the observed element concentrations in these excipients to the ICH Q3D Option 1 concentrations, for most excipients, the mass of excipient delivered to the patient would typically need to exceed 10 g in order for the elemental impurity level in the drug product to exceed the Q3D Option 1 limit.

As additional data become available, trends in elemental impurities levels in excipients may emerge, but it is important to stress that this survey only provides a snapshot of elemental impurity levels in a limited number of pharmaceutical materials from certain suppliers. No conclusions can be drawn from these data that preclude the need for pharmaceutical manufacturers to perform a risk assessment with the suppliers and grades of excipients used in their drug products. Additionally, the limited number of samples tested in this study may not

Table 7. Class 3 Elemental Impurity Concentrations in Excipient Samples Concentrations given as <LOD Indicate Levels Below the Method Limit of Detection

N (Number of Samples)	Materials Name	Li (ppm)	Sb (ppm)	Ba (ppm)	Mo (ppm)	Cu (ppm)	Sn (ppm)	Cr (ppm)
5	Ferric oxide red	0.15 ± 0.10	0.13 ± 0.10	1.04 ± 1.66	2.47 ± 0.88	13.0 ± 8.9	4.41 ± 4.51	32.5 ± 10.8
5	Ferric oxide yellow	<LOD	0.17 ± 0.16	0.41 ± 0.07	2.87 ± 1.87	12.4 ± 7.1	2.47 ± 1.04	26.2 ± 12.0
5	Ferrous oxide black	0.05 ± 0.00	0.17 ± 0.00	2.00 ± 3.06	0.82 ± 0.00	5.60 ± 0.02	0.78 ± 0.00	7.94 ± 0.09
11	Talc	2.47 ± 1.58	0.01 ± 0.02	6.88 ± 11.96	0.35 ± 0.72	0.10 ± 0.21	0.24 ± 0.16	9.86 ± 9.51
7	Titanium dioxide	0.05 ± 0.01	0.01 ± 0.02	14.8 ± 32.7	0.40 ± 0.25	0.17 ± 0.27	0.25 ± 0.14	0.92 ± 0.25
3	Silicon dioxide	<LOD	0.03 ± 0.01	0.86 ± 0.80	0.13 ± 0.09	0.05 ± 0.05	<LOD	1.82 ± 0.97
13	Calcium phosphates	0.39 ± 0.41	0.10 ± 0.05	2.11 ± 1.76	2.60 ± 1.06	0.15 ± 0.15	0.01 ± 0.01	5.11 ± 5.99
5	Carrageenan	0.11 ± 0.03	0.01 ± 0.00	1.73 ± 0.57	0.05 ± 0.02	0.33 ± 0.13	0.01 ± 0.01	0.31 ± 0.14
26	Calcium carbonate	0.16 ± 0.04	0.01 ± 0.01	19.9 ± 22.7	0.01 ± 0.05	0.36 ± 0.13	0.00 ± 0.00	3.64 ± 0.50
17	Sodium alginate	0.10 ± 0.14	0.02 ± 0.02	59.4 ± 70.3	0.21 ± 0.15	0.36 ± 0.90	0.03 ± 0.05	0.83 ± 0.45
9	Silicone elastomer	<LOD	0.00 ± 0.00	0.13 ± 0.13	<LOD	<LOD	<LOD	0.11 ± 0.06
9	Simethicone	<LOD	<LOD	0.04 ± 0.03	0.02 ± 0.00	0.01 ± 0.01	0.09 ± 0.00	0.19 ± 0.02
9	Simethicone emulsion	<LOD	<LOD	0.04 ± 0.01	0.26 ± 0.05	0.05 ± 0.01	0.09 ± 0.04	2.21 ± 0.42
6	Dimethicone	<LOD	<LOD	<LOD	<LOD	<LOD	0.03 ± 0.08	0.03 ± 0.04
3	Silicone tacky gel	<LOD	<LOD	<LOD	<LOD	<LOD	0.02 ± 0.02	0.01 ± 0.01
3	Polydimethysiloxane	<LOD	0.01 ± 0.02	0.00 ± 0.00	<LOD	<LOD	0.09 ± 0.16	<LOD
17	Povidone	<LOD	0.00 ± 0.00	0.03 ± 0.06	0.01 ± 0.02	0.00 ± 0.01	0.01 ± 0.03	0.01 ± 0.01
3	Ethylcellulose	0.01 ± 0.01	<LOD	0.53 ± 0.28	<LOD	0.24 ± 0.06	<LOD	0.08 ± 0.04
11	Carboxymethylcellulose	0.06 ± 0.15	0.00 ± 0.00	1.16 ± 0.91	0.04 ± 0.05	0.03 ± 0.04	0.05 ± 0.08	0.20 ± 0.09
8	Hydroxypropylcellulose	0.00 ± 0.01	<LOD	0.14 ± 0.18	0.01 ± 0.02	0.05 ± 0.07	0.08 ± 0.05	0.07 ± 0.09
6	Hypromellose	0.01 ± 0.01	<LOD	0.19 ± 0.03	0.07 ± 0.06	0.02 ± 0.02	0.15 ± 0.24	0.60 ± 0.29
1	Zinc stearate	<LOD	<LOD	37.49	<LOD	<LOD	<LOD	0.02
1	Magnesium stearate NF/EP	0.03	<LOD	0.11	<LOD	<LOD	<LOD	0.02
1	Magnesium hydroxide granular	0.00	0.11	0.08	2.60	1.08	0.05	0.02
1	Magnesium carbonate	<LOD	0.01	0.22	0.06	<LOD	<LOD	0.94
1	Blue #1	0.07	0.00	0.10	1.10	0.49	<LOD	0.61
1	Red #27 Al.Lake	0.03	0.01	11.65	0.41	5.45	0.28	2.38
1	Imidurea	<LOD	<LOD	0.01	<LOD	<LOD	<LOD	0.03
1	N-Methyl-2-pyrrolidone	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
1	2,5-Dioxo-4-imidazolidinyl	<LOD	<LOD	0.00	<LOD	0.06	0.03	<LOD
3	Tetracaine HCl	<LOD	<LOD	0.14 ± 0.24	<LOD	<LOD	<LOD	0.03 ± 0.01
3	Orphenadrine citrate	<LOD	<LOD	0.15 ± 0.26	<LOD	<LOD	<LOD	0.03 ± 0.03
2	Procainamide HCl	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0.02 ± 0.00
3	Benzonatate	<LOD	<LOD	0.00 ± 0.00	<LOD	<LOD	<LOD	0.01 ± 0.02
1	Flunixin meglumine	<LOD	<LOD	<LOD	0.14	<LOD	<LOD	0.52
1	Bismuth subsalicylate	0.04	0.00	<LOD	<LOD	<LOD	<LOD	0.10
1	Carbonyl iron	0.04	<LOD	0.04	37.58	<LOD	<LOD	9.13
1	Bemotrizinol	0.01	<LOD	<LOD	<LOD	<LOD	<LOD	0.00

Concentrations given as 0.00 indicate levels below the stated precision but above the LOD. Uncertainties given as 0.00 are below the stated precision. The bottom 8 rows display results for some drug substances.

reflect the natural variability of elemental impurity levels for some materials. In particular, some mined excipients are known to exhibit relatively large excursions over time from mean levels of certain elemental impurities.

This survey presents determinations of 24 elements in 205 pharmaceutical materials for a total of more than 4900 determinations. Quality control samples and system suitability procedures were used throughout the survey to assure the accuracy of the results. Although a full uncertainty budget is out of scope for this survey, certain considerations for minimizing measurement error from instrumental sources and sample preparation sources are discussed below.

Inductively coupled plasma mass spectrometry provides extremely low detection limits, ranging from part per trillion (ppt) to part per billion (ppb) for many elements. It is a sensitive and selective technique that is quantitative and has acceptable precision at concentrations that are suitable to demonstrate compliance with safety-based PDEs for many pharmaceutical products. The most challenging shortcoming of ICP-MS is the existence of non-spectroscopic and spectroscopic interferences for some elements. These interferences are generally known, and strategies have been or can be developed to overcome these challenges. To reduce the matrix interferences, calibration standards or matrix blanks should be prepared in the same matrix as the samples. When feasible, dilution factors in the range of 50–100 may assist to minimize the influence of the sample to matrix effects. Argon background interference and oxygen-, nitrogen-, and hydrogen-containing interferences are significant because of their constant introduction to the system. In some cases, these interferences can be avoided by judicious selection of analytical isotope. Polyatomic interferences which result from samples containing sodium, halogen, carbon,

and oxygen can be decreased by collision or reaction cells. Collision cells are based on the observation that polyatomic ions undergo more collisions than atomic ions when exposed to low pressure helium, which deflects the interferent out of the detection path. This survey also demonstrates that elements with known interferences exhibit higher LODs and greater variability in quality control samples than elements that are less likely to have interferences.

Recovery of elemental impurities from the sample matrix is a challenging consideration for analysis of pharmaceutical materials. Microwave-assisted digestion provides an approach to sample preparation which can be used to assess the maximum mass of an elemental impurity that may be delivered to a patient in a specified drug product. In this study, digestion of excipients such as silicon dioxide, titanium oxide, and talc utilized HF to maximize dissolution of the solid matrix. Additional safety precautions must be exercised when HF is used. Concern over the safe handling of HF prompted a review of the recovery of elemental impurities with and without HF in a spiked sample of talc that is not expected to be totally solubilized by HNO_3 digestion. Mg and Si spike recoveries were 800% and 5000%, respectively, indicating that the observed levels of these elements were elevated because of decomposition of the magnesium silicate structure of the material in the presence of HF. On the other hand, most elements that were expected to be present as extraneous impurities exhibited recoveries in the 90%–110% range under both conditions, indicating that unbound elemental impurities can be adequately analyzed without the use of HF in talc. Although further investigation is required, these results indicate that HF may be of limited use when analyzing elemental impurities in hard-to-digest materials.

A number of element-specific precautions are also warranted when analyzing complex products for numerous elements, such as is required in the analysis of USP <232> or ICH Q3D elemental impurities. When boron is of interest, it is known that carry over can occur from boron's tendency to volatilize as boric acid from the sample solution inside the spray chamber.[9] It is also well known that Hg may volatilize and be absorbed in the ICP sample introduction system, which can require a long wash out time and increase Hg background levels. For this reason, the concentrations of Hg standards were minimized in this study. In addition, Hg is typically stabilized in solution through the addition of HCl in the digestion matrix. Au has also been used as a Hg stabilizer, though there is some controversy over the relative merits of Au and Cl for Hg stabilization.[10] Finally, some researchers have reported that facile oxidation of Os to the volatile and toxic OsO_4 oxide can result in challenges during the quantitative determination of Os.[11] The volatile nature of this oxide can also result in carry over. It has been proposed that aqua regia provides a better matrix for Os recovery in some cases.[11]

CONCLUSIONS

This survey covers 24 elements in 205 samples for a total of over 4900 determinations. The results shown in Table 3 suggest that these determinations are accurate. Overall, low levels of elemental impurities were found in the synthetic excipients examined in this survey, as well as excipients such as celluloses that are highly processed before use. Some mined excipients exhibit relatively elevated levels of elemental impurities compared with other materials examined in this survey, but in many cases these levels were still low in comparison with relevant PDEs. Although this survey provides some evidence that elemental impurity levels in excipients are not likely to result in excessive levels in drug products, these results cannot be considered definitive. Lot-to-lot and supplier-to-supplier variability have not been addressed thoroughly in this survey. As noted above, no conclusions can be drawn from these data that preclude the need for pharmaceutical manufacturers to perform a risk assessment with the suppliers and grades of excipients used in their drug products.

ACKNOWLEDGMENTS

This project was supported in part by an appointment (G.L.) to the Research Participation Program at the Center for Drug Evaluation and Research administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the U.S. Department of Energy and the U.S. Food and Drug Administration.

REFERENCES

1. United States Pharmacopeia and National Formulary (USP 38-NF 33). Chapter <231>, Heavy metals. Accessed August 26, 2015, at: www.usp.org.

2. Blake KB. 1995. Harmonization of the USP, EP and JP heavy metals testing procedures. USP Pharmacopeial Forum 21(6):1632.

3. European Medicines Agency, Committee for Medicinal Products for Human Use. 2008. Guideline on the specification limits for residues of metal catalysts or metal reagents. Doc. Ref. EMEA/CHMP/SWP/4446/2000

4. Wang T, Wu J, Jia X, Bu X, Santos I, Egan RS. 2003. An atomic spectroscopic method as an alternative to both USP heavy metal <231> and USP residue on ignition <281>. Stimuli to the revision process. USP Pharmacopeial Forum 29(4):1328–1336.

5. Geary JT. 2004. Changes to USP general chapter heavy metals <231>. Stimuli to the revision process. USP Pharmacopeial Forum 30(5).

6. Schenkenberger M, Lewen N. 2004. Inductively coupled plasma–optical emission spectroscopy as an alternative to the heavy metals test. Stimuli to the revision process. USP Pharmacopeial Forum 30(6).

7. The United States Pharmacopeia. 2011. Elemental impurities-limits <232>. In process revision. USP Pharmacopeial Forum 37(3).

8. International Conference on Harmonization. 2009. Final Concept Paper Q3D: Impurities: Guideline for elemental impurities. Accessed August 26, 2015. www.ich.org.

9. Al-Ammar AS, Gupta RK, Barnes RM. 2000. Elimination of boron memory effect in inductively coupled plasma-mass spectrometry by ammonia gas injection into spray chamber during analysis. Spectrochim Acta Part B 55:629–635.

10. Alliborn J, Fatemian E, Walker PJ. 1999. Determination of mercury in potable water by ICP-MS using gold as a stabilizing agent. J Anal At Spectrom 14:235–239.

11. Van Hoecke K, Catry C, Vanhaecke F. 2012. Optimization of sample preparation and a quadrupole ICP-MS measurement protocol for the determination of elemental impurities in pharmaceutical substances in compliance with USP guidelines. J Anal At Spectrom 27:1909–1919.