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Research Article

Clean Chemistry for Elemental Impurities Analysis of Pharmaceuticals in Compliance with USP 232

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Abstract. United States Pharmacopeia updated its 100 years old metal analysis method with inductively coupled plasma mass spectrometry (ICP-MS) and inductively coupled plasma optical emission spectrometry (ICP-OES). These sensitive instruments require that sample preparation be at least as sophisticated as the instrumentation used in the analysis. Sample contamination during sample preparation has to be controlled to an acceptable level given the low detection limit of these instruments and the ubiquitous presence of elements. This article focused on sample contamination during sample preparation. Contaminations from environment, reagents, and lab apparatus were investigated for their impact on trace element analysis. Advice on clean lab practice was offered to the pharmaceutical industry in regard to contamination control in elemental analysis labs at a time when the industry is preparing for compliance with elemental impurities in drug products.

KEY WORDS: contamination; elemental impurities; ICP-MS; pharmaceutical analysis; trace analysis.

INTRODUCTION

Toxic elements in drug products present a threat to the public health. Regulatory agencies around the world mandate that the pharmaceutical industry must monitor and control toxic elements to acceptable levels. Recently, the United States Pharmacopeia (USP) updated General Chapters 232 and 233 with the implementation date of 1 January 2018 (1). These chapters address elemental impurities issue through modern analytical instrumentations such as inductively coupled plasma mass spectrometry (ICP-MS). ICP-MS is capable of sensitive detection of elemental impurities at trace levels (ICP-MS has an instrument detection limit normally below 1 ppt). The lower detection limit of ICP-MS, combined with its superior measurement specificity and ability to measure multiple elements at the same time, makes ICP-MS the top choice of element analyzers for pharmaceutical companies seeking for elemental analysis capacity to meet the new elemental impurities requirements from USP (2).

The concentration limits in USP 232 and ICH Q3D push the boundary of analytical instrumentation to lower detection limit. At the same time, the use of modern instrumentation, particularly ICP-MS, puts extra burden on laboratories and analysts because elemental impurities are generally present at trace levels that requires more attention to sample contamination during sample collection, storage, preparation, and measurement. Trace amounts of analyte elements are ubiquitous in the environment. The issue of sample contamination becomes increasingly dominating when an analyst strives to reach lower detection limit. As an example, in the semiconductor industry where detection of ultra-trace elements as low as parts per quadrillion level is desired, a class-100 or better clean room equipped with high-efficiency particulate air (HEPA) filters is required to house both sample preparation and the ICP-MS instrument (3). In the pharmaceutical industry, it is controversial to build a clean room for compliance with elemental impurities. Most trace element analyses of pharmaceuticals are performed in ordinary laboratory environments. Lab cleanliness and the practice of clean laboratory techniques cannot be overemphasized in order to achieve method accuracy, precision, and robustness. The sources of contamination in an elemental analysis lab can be broken into the following: reagent, air, lab apparatus, labware, and even the analyst. Determination of trace elements at parts per billion levels can be biased by contamination from any of these sources (4). An effective approach towards contamination control is to evaluate each of these sources. The objectives of this article are to quantify the level of contamination from these sources in a typical lab (neither clean room nor clean bench is installed) and provide practical suggestion how to control contamination in ICP-MS analysis. The clean lab practices discussed in this study are expected to offer insight into common contamination issues in elemental impurities analysis, particularly for pharmaceutical companies who lack a strong training or background in trace element analysis while trying to prepare for compliance with USP 232. This article is of general interest to lab operations and does not cover analytical method development and validation.

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EXPERIMENTAL

Laboratory Environment

The laboratories housing elemental impurities analysis were modified from traditional laboratories to accommodate the needs for gases and exhaust ventilation. One laboratory was dedicated to sample preparation and closed-vessel microwave digestion. The ICP-MS instruments were placed in a separate laboratory shared with other analytical instruments. Laboratory air was conditioned through a centralized ventilation and air conditioning system equipped with a coarse particle filter that is changed every year. As part of the effort trying to clean the air supplied to the sample preparation laboratory, air vents on the laboratory ceiling were covered with coarse particle filter. Rusty pipes, pillars, cabinets, sinks, and other metal structures were either replaced or covered for the rust. Neither clean room nor clean bench was equipped in the lab for trace element analysis. Concentrated acids were handled in standard fume hoods. Bottle-top pipettes were used to dispense concentrated acids. Sample and standard preparation using diluted acids were performed on open bench. All solutions were either capped or covered with paraffin film (Parafilm®) to minimize exposure to atmosphere.

Instrumentation

ICP-MS. Elemental analysis performed in this study used iCAP Qc ICP-MS instrument from Thermo Scientific (Bremen, Germany) operating at kinetic energy discrimination (KED) mode. The instrument was qualified for its intended use by following the vendor's protocol for installation, operation, and performance qualification (IQ/OQ/PQ). Instrument performance was verified for its sensitivity and stability every day prior to data collection on any sample. The major parameters used for instrument operation are listed in Table I.

Microwave Digestion. CEM SP-D Discover microwave digestion system (Matthews, NC) equipped with an Explorer auto-sampler was used for closed-vessel acid digestion. The 35-ml digestion vessel is made from Pyrex glass and sealed with a Teflon-lined silicone cap. They are capable of sustaining temperature up to 240°C and pressure of 500 PSI.

Freezer Mill. A cryogenic mill (SamplePrep freezer/mill model 6870D, SPEX, Edison, NJ) was used for homogenizing capsule products and some coated tablet products. The grinding vial set, including a cylinder, an impactor, and two end plugs, is constructed from polycarbonate materials. Metal parts in direct contact with samples are excluded due to contamination with several elements including nickel.

Reagent

Microwave-assisted acid digestion is recommended for pharmaceutical sample preparation for elemental impurities analysis. High-purity acids play an important role in achieving low detection limits. Ultrapure acids (HNO_3 and HCl, Optima grade, Fisher Scientific) were used for acid digestion, standard preparation, labware cleaning, and preparation of ICP-MS solutions (internal standard, rinse solution, tuning solution, detector setup solution). Hydrofluoric acid (HF) was not used due to safety concern over this acid. Deionized water (DI water) used for solution preparation and labware cleaning was supplied by Milli-Q water purification systems that are maintained semi-annually (Merck Millipore, Billerica, MA). DI water quality met ASTM Type I standard with a resistivity of 18.2 megaohm.cm at 25°C.

Table I. Major ICP-MS Operating Parameters

Parameter	Value
RF power	1500 W
Nebulizer	PFA Standard MicroFlow (optimal sample uptake rate 400 µl/min)
Spray chamber	Quartz cyclonic type
Cone interface material	Nickel
Plasma gas flow	14 l/min
Auxiliary gas flow	0.8 l/min
Nebulizer gas flow	1.0 l/min
Analyte	51V, 59Co, 60Ni, 65Cu, 75As, 95Mo, 101Ru, 103Rh, 105Pd, 114Cd, 189Os, 193Ir, 195Pt, 202Hg, 208Pb
Internal standards	45Sc, 89Y, 115In, 159Tb, 209Bi

RF radio frequency, *PFA* perfluoroalkoxy

Standard

Aqueous standard stock solutions that contain the target elements were purchased from Inorganic Ventures (Christiansburg, VA). All standard stocks are traceable to NIST Standard Reference Materials and came with a Certificate of Analysis. Working standards (J solutions) used for ICP-MS calibration were diluted from concentrated stock solution with a diluent (5% nitric acid/1% HCl/94% water (*v*/*v*/*v*)).

Solution Container

Volumetric flasks of various sizes made from polymethylpentene (PMP) were used for standard and sample preparation. Polypropylene tubes of 50 ml were used for temporary storage and transfer of standards and samples. Microwave digestion used 35-ml borosilicate Pyrex glass vessels sealed with Teflon-lined plastic caps. All containers, including pipette tips and transfer pipettes, were rinsed thoroughly with DI water or diluent prior to use.

Statistical Analysis

Due to the inherent variability in sample preparation and ICP-MS analysis, replicate samples were prepared independently to capture measurement uncertainty. Whenever elemental concentrations were plotted in bar graphs for comparison between different treatments (for example, contaminated sample *vs.* un-contaminated control sample), 95% confidence intervals were calculated for the mean concentrations assuming data normality distribution. The 95%

confidence interval is plotted as the error bar in all bar graphs. The error bars provide visual comparison of the means among different treatments. Statistical tests such as Student's *t* test or analysis of variance were considered unnecessary and not performed. Non-overlapping of the error bars (95% confidence intervals) between two treatments indicates that the difference in the mean concentrations is statistically significant. Excel spreadsheet functions were used for calculation of 95% confidence intervals. The function for 95% confidence interval calculation is 1.96×standard error of the mean (SEM) where SEM=standard deviation/sqrt (*n*) (*n*=sample size).

RESULTS AND DISCUSSION

ICP-MS Calibration and Detection Limit

ICP-MS was calibrated using a series of working standard solutions freshly prepared before sample analysis. The working standard solutions span a concentration range from 0.5 J to 2 J as defined by USP 233. Calibration is deemed successful when the coefficient of determination (R^2) of the calibration line is not less than 0.99.

A generic ICP-MS method was developed and validated for pharmaceutical analysis. The same method was also used in this clean chemistry study. The capacity of this generic method in detecting trace contaminants is reflected by method detection limit (MDL). MDL is defined here as ten times of the instrument detection limit (IDL). IDL is three times of the standard deviation of six replicate measurements of the calibration blank (*i.e.*, the diluent used to prepare J solutions). Since MDL changes with instrument condition such as interface cone deposition and pump tubing wear, there is a slight fluctuation in the day-to-day MDL values. The averages of MDLs obtained during this study are shown in Table II. MDL values provide guidance to the capability of the generic ICP-MS method in detecting trace level contaminants. They were not verified experimentally. The method reports "n.d." (not detectable) in the tabulated results if the measurement is below MDL. The concentrations are reported "as it is" in graphs for illustration purpose where negative concentrations are generally treated as n.d. For most target elements, this method achieves sub-parts per trillion detection limits. The high MDL of molybdenum most likely results from the high residual in concentrated acids.

Water Quality

The importance of water quality in trace elemental analysis cannot be overemphasized. For elemental impurities compliance, DI water quality meeting ASTM Type I requirement is considered sufficient. DI water needs to be monitored constantly for its resistivity and total organic carbon (TOC) level, with acceptance criteria resistivity not less than 18 megohm cm at 25°C and TOC not more than 10 ppb. For information purpose, we measured 10 independent DI water samples and compared their elemental impurities to 10 independent tap water samples in Table III. Most target elements are not detectable in DI water. Copper has a concentration 2.088 μg/l. However, this concentration is considered insignificant as compared to the copper concentration 300 μg/l at 1 J level (Note: 1 J is defined here based on a dilution factor of 1000, *i.e.*, 1 mg sample dissolved in 1 ml diluted acid solution.).

Contamination from Sampling

Sampling is defined here as presenting an appropriate amount of sample representative of the pharmaceutical material under study for sample preparation. Once a sample is received, the analyst should take caution not to contaminate the sample when opening the package, dispensing, homogenizing, and weighing the sample. In most cases of solid dosage form sampling, the unit dose far exceeds the capability of microwave digestion and ICP-MS instrument and weighing a homogeneous sample in the form of powder is required. A variety of apparatus exist for pulverizing and homogenizing tablets and capsules, including mortar and freezer mill. Freezer mill is able to homogenize capsule products. To evaluate contamination from sample pulverization, a tablet product with a nominal unit weight of 138 mg was ground into fine powder using two different methods: glass mortar and freezer mill. For each pulverization method, 10 powder samples each of 138 mg were prepared using a generic approach applicable to most pharmaceutical materials with excellent method robustness: The powder sample was solutionized completely in a mixture of 5 ml concentrated HNO_3 and 1 ml concentrated HCl by closed-vessel microwave digestion; Microwave digestion was performed at 200°C with a holding time of 5 min; And digest was transferred into 100-ml PMP flask and diluted with water. An aliquot was then transferred into a 14-ml polypropylene test tube for ICP-MS analysis. For comparison, 10 intact whole tablets were also prepared and analyzed for the target elements using the same generic method.

Side-by-side comparison of these three different sampling methods can be seen in Fig. 1. Contamination from sample pulverization is low even for copper and nickel. There is no statistically significant difference in these three sampling methods with regard to the level of contamination.

Contamination from Microwave Apparatus

Pyrex glass vessel can be used for closed-vessel microwave digestion as long as HF acid is not used and rigorous cleaning procedure is followed. The cleanliness of digestion vessel, stirring bar, and vessel cap was subject to extra scrutiny because of the readiness of contaminants leaching into concentrated acid mixture under high temperature and pressure.

Table II. Method Detection Limits in Micrograms per Liter

	51V	59Co	60Ni	65Cu	75As	95Mo	101Ru	103Rh	105Pd	111Cd	189Os	193Ir	195Pt	202Hg	208Pb
MDL	0.021	0.001	0.011	0.007	0.006	0.229	0.001	0.001	0.005	0.001	0.005	0.014	0.001	0.001	0.001

MDL method detection limit

Table III. Concentrations (μg/L) of Target Elements in DI Water and Tap Water

	51V	59Co	60Ni	65Cu	75As	95Mo	101Ru	103Rh	105Pd	111Cd	189Os	193Ir	195Pt	202Hg	208Pb
DI water	n.d.	0.017 (0.005)	n.d.	2.088 (2.670)	n.d.	n.d.	0.080 (0.045)	n.d.	n.d.	n.d.	0.068 (0.078)	n.d.	0.002 (0.001)	0.007 (0.006)	n.d.
Tap water	0.044 (0.011)	0.134 (0.009)	13.475 (1.283)	485.342 (168.85)	0.142 (0.003)	0.444 (0.697)	0.019 (0.007)	n.d.	n.d.	0.041 (0.016)	0.027 (0.028)	0.479 (0.946)	n.d.	0.005 (0.003)	0.270 (0.093)

The numbers in parentheses are standard deviations of measurements from 10 independent samples (n=10)
DI water deionized water, *n.d.* not detectable

We have identified Teflon-coated stirring bar as the culprit of cobalt contamination. Glass-encapsulated stirring bar should be used with microwave digestion whenever HF acid is not required for total extraction.

The microwave system uses Teflon-lined plastic cap to seal and vent the digestion vessel during closed-vessel digestion. To evaluate cap cleanliness, we soaked 50 caps overnight in two different extraction media: 500 ml DI water and 500 ml 10% nitric acid. The solutions were then analyzed for impurities. The concentrations of the target elements found in extraction solutions are compared to those found in the control samples which are 10% nitric acid stored in pre-cleaned PMP flask. The comparison is shown in Fig. 2. Given the significantly high concentration of nickel, copper, and lead extractables from caps in 10% nitric acid, it is suggested that the caps be soaked in 10% nitric acid overnight and rinse with DI water at least three times before use with digestion vessel for microwave digestion.

Contamination from Pyrex digestion vessel was also evaluated by an extractables study. We filled 10 new 35-ml digestion vessels with 30 ml 10% nitric acid and let the vessels sit on bench overnight. Target elements in the extraction media were analyzed and the results are shown in Fig. 3 along with the results from the control samples. The control samples are 10% nitric acid stored in a PMP flask. Copper, arsenic, and lead show a significantly higher concentration in the extraction media as compared to the controls, which indicates the potential contamination with these elements from digestion vessel. It is recommended that the Pyrex digestion vessels be soaked in diluted nitric acid overnight and then be rinsed with DI water before their use for microwave digestion. Method blanks show that contamination from repeated use of Pyrex vessels is insignificant for the USP 232 target elements. Pyrex glass vessel, without the Teflon liner, can be used for acid digestion as long as the vessel is properly cleaned prior to use. It is contrary to the common perception of "dirty" glass digestion vessels as compared to the "cleaner" quartz or Teflon vessels.

Contamination from Plastic Container

Plastic containers made from various materials such as polyethylene (PE), perfluoroalkoxy (PFA), polymethylpentene (PMP), and polypropylene (PP) are widely used in elemental analysis labs for sampling and storage because of their cleanliness and compatibility with HF acid. Contamination from plastic container, although less severe than other container types, is worthy of study (5). We tested the cleanliness of 14-ml PP test tubes used with ICP-MS autosampler. Before being filled with diluent, the test tubes were cleaned in two different ways: DI water rinsing and soaking in 10% nitric acid overnight and then DI water rinsing. Target elements found in diluent are shown in Fig. 4, along with the elements found in diluent filled directly into test tubes that were not treated. There is nickel contamination from the untreated test tubes, but the contamination level is significantly reduced by tube cleaning. It is interesting to see that the acid soaking followed by DI water rinsing brings about the same cleanliness as DI water rinsing alone. It seems that DI water rinsing is sufficient for PP test tube cleaning. Similar results were also observed for 50-ml PP conical sample tubes and are

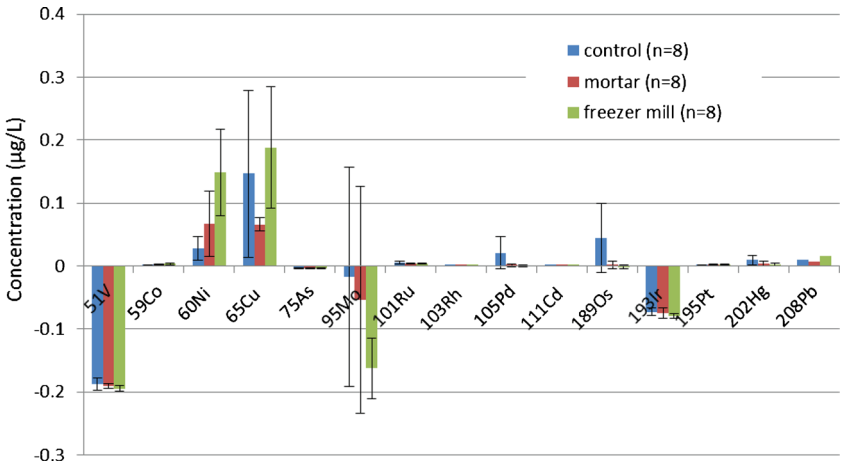

Fig. 1. Concentration of target elements in a tablet product which was processed by three different sampling methods: whole tablet (control sample), tablet pulverized by mortar, and tablet pulverized by freezer mill. *Error bar* represents 95% confidence interval of the mean (sample size n=8)

not shown here. PMP flasks and PFA beakers were not studied for their cleaning, but method blanks have not shown any significant contamination when we used these plastic containers and employed a DI water rinsing cleaning procedure for them. For USP 232 compliance purpose, contamination from plastic containers is considered low and does not impact method capacity. However, it does not exclude acid soaking as an ultimate cleaning method when lower detection limit is needed. For new containers, plastic or glass, acid soaking followed by thorough DI water rinsing is always recommended before their first use.

Contamination from Lab Supplies

Any lab supply, such as gloves, wipes, Parafilm, pipette tips, and transfer pipettes, can be a potential source of element contamination if they come in indirect or direct contact with sample. We evaluated two brands of powder-free nitrile gloves used in our labs: small-size Kimberly-Clark exam gloves and small-size High Five gloves. One glove was dipped and rinsed several times in 100 ml 10% nitric acid in a PFA beaker. Rinsates were analyzed for the target elements and the results are shown in Fig. 5 along with the element concentrations in the control samples. Control samples are 10% nitric acid stored in a pre-cleaned PFA beaker. The High Five gloves exhibit very high level of surface contamination especially with lead. Glove surface was also contaminated with arsenic and cadmium. By contrast, Kimberly-Clark gloves show significantly less contamination. Cleaner clean room gloves are commercially available for elemental analysis. In any case, an analyst should use DI water to thoroughly rinse their gloves before working in the lab.

Contamination from Parafilm, Kimwipes, and Scott towels was also evaluated in an extractable study because they came in direct or indirect contact with samples. One 10 cm×30 cm Parafilm was soaked in 50 ml 10% nitric acid

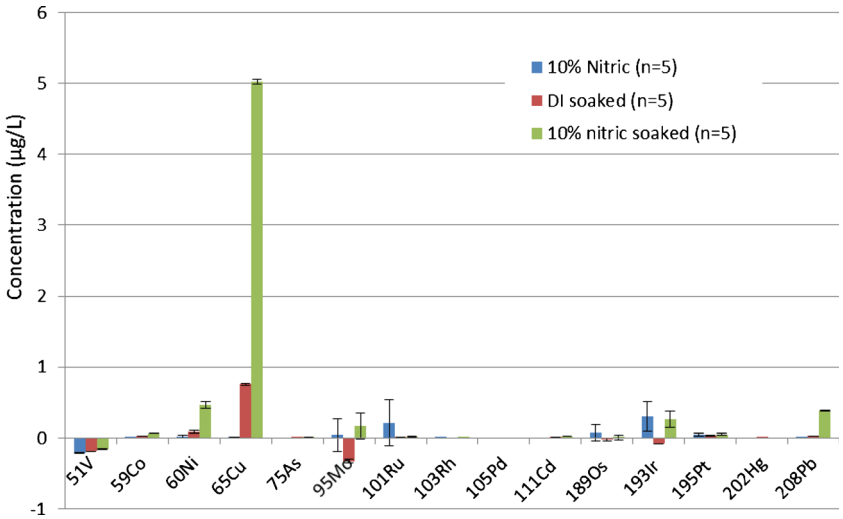

Fig. 2. Concentration of target elements in 10% nitric acid stored in pre-cleaned PMP flask, as compared to impurities in 10% nitric acid after soaking digestion vessel caps overnight, and impurities in DI water after soaking digestion vessel caps overnight. *Error bar* represents 95% confidence interval of the mean (n=5)

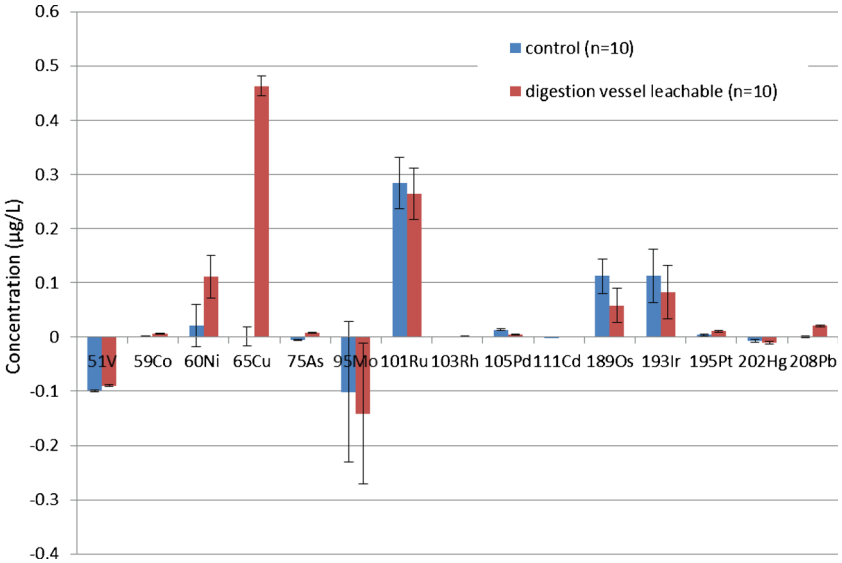

Fig. 3. Concentration of target elements extracted from Pyrex digestion vessel using 10% nitric acid. The significance of extractables can be evaluated by comparing to the concentration of these elements in the same 10% nitric acid extraction media stored in a pre-cleaned PMP flask. *Error bar* represents 95% confidence interval of the mean (n=10)

for 30 min. One ply of 11 cm×21 cm Kimwipes was soaked in 50 ml 10% nitric acid for 30 min. One ply of Scott c-folded paper towel was soaked in 50 ml 10% nitric acid for 30 min. All extraction media were then sampled and analyzed for target elements. Figure 6 shows the concentrations of target elements in the extraction media for each material. Control sample is 10% nitric acid stored in a PFA beaker. Scott paper towel shows very high level of vanadium, cobalt, nickel, copper, and lead in its extractables. Although these extractables are not readily going to samples, Scott paper towel is considered dirty and presents a potential contamination source. Kimwipes is much cleaner, but still shows a high concentration of nickel and copper in its extractables. Its direct contact with sample should be avoided. Thus, using Kimwipes for cleaning and drying should be limited, if cannot be avoided, in elemental analysis lab. Air drying is preferred for wet containers. None of the target elements is detectable in Parafilm extractables and control samples. Parafilm is considered clean and suitable for use in elemental analysis lab.

Contamination from Laboratory Atmosphere

Contamination from dust and airborne particles in an elemental analysis lab has long been identified (6). While a clean room facility is usually recommended by authorities for trace element analysis (7), the lab should always makes its decision by evaluating air contamination and its effect on lab operation through air monitoring or experiment. To evaluate the contribution of lab air to elemental impurities contamination, we placed two 500-ml PFA beakers side-by-side on the bench of sample preparation lab. Both beakers were filled with 100 ml 10% nitric acid. One beaker was open to air while

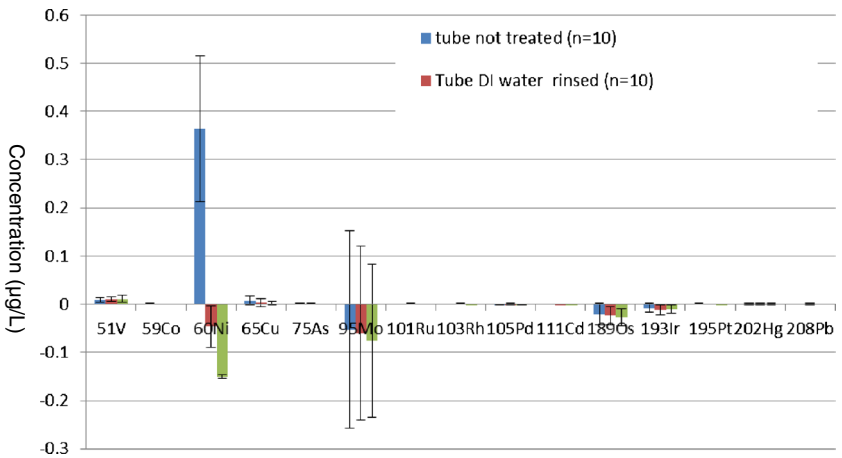

Fig. 4. Target elements in diluent in ICP-MS test tubes that were cleaned using three methods: tubes were not treated (*blue bars*); tubes were cleaned by DI water rinsing (*red bars*); and tubes were cleaned by acid soaking overnight and then rinsed with DI water (*green bars*). *Error bar* represents 95% confidence interval of the mean (n=10)

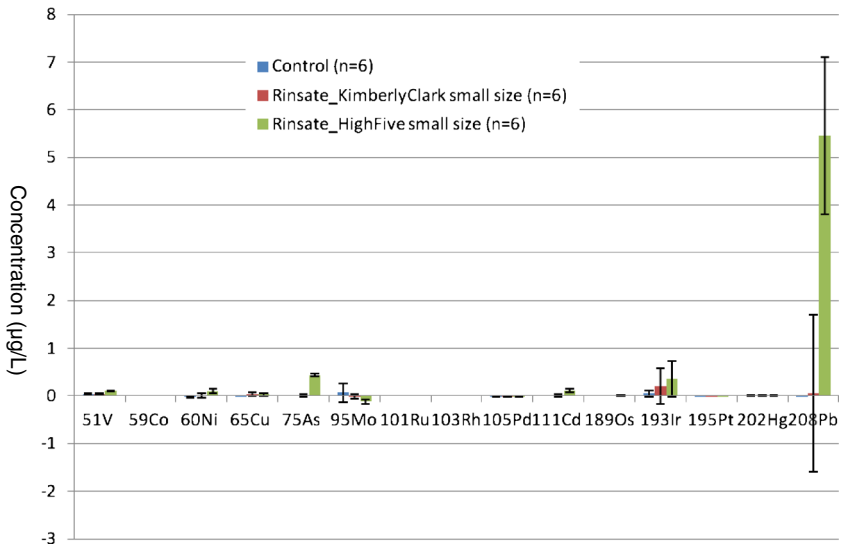

Fig. 5. Elemental impurities in 10% nitric acids used to rinse two common brands of laboratory gloves. Control samples are 10% nitric acid stored in a PFA beaker. *Error bar* represents 95% confidence interval of the mean (n=6)

the other was covered with Parafilm. After 5 days, the solutions from both beakers were aspired directly to ICP-MS and analyzed for target elements. The results are shown in Table IV in relative amounts. To correct for solution volume change caused by evaporation, all measured concentrations were normalized to osmium since osmium, if present, has extremely low concentration in air (8). As compared to the control which is the solution isolated from air, the solution exposed to air shows elevated elemental composition, especially for lead whose concentration is five times higher and iridium whose concentration is eight times higher. For laboratories located in polluted area or for laboratories having high dust level, lead contamination may become even more severe, which would require installation of a laminar flow hood or a clean bench. Clean bench supplies the work area with air cleaned by HEPA filter. HEPA filters are 99.97% efficient in removing particles down to 0.3 µm (9). In any case, exposure of the solution to air should be minimized by capping the containers or covering the containers with Parafilm.

Contamination from Analyst

Careless handling of standard and sample can cause serious contamination. Touching of the surface that may come into direct contact with solution can result in contamination with a number of elements including sodium, chlorine, calcium, and lead. A study of lead contamination from human fingers showed an average of 3.1 µg of lead in 15 ml 1 N nitric acid after soaking two fingers for 2 min (10). Cosmetics, hair dyes, and jewelry are known to cause contamination in trace element analysis (11). The analyst must be careful in handling standards. Direct pipetting from standard bottle should be avoided to minimize cross contamination. Standard solution must be mixed thoroughly when preparing concentrations at parts per billion or lower level. The analyst must be aware of the history of labwares and rigorous cleaning has to be performed before vessels exposed to high concentrations can be used for trace element analysis.

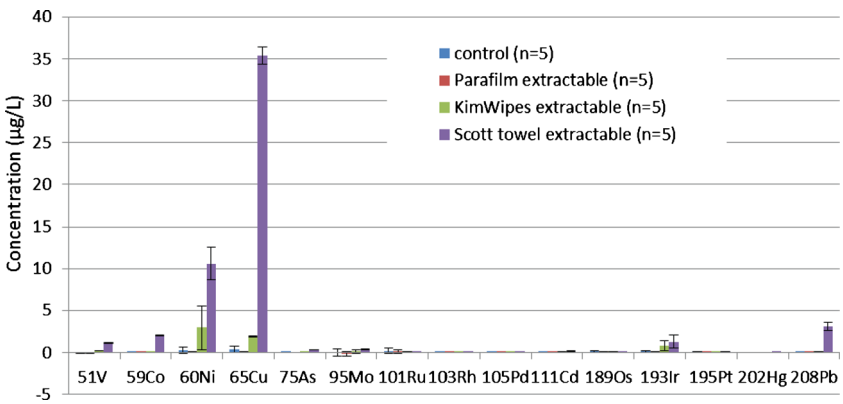

Fig. 6. Elemental impurities in extractables from Parafilm, Kimwipes, and Scott towel. Control is 10% nitric acid used as extraction media. *Error bar* represents 95% confidence interval of the mean (n=5)

Table IV. Relative Amount of Target Elements in 10% Nitric Acid After Exposure to Air

	51V	59Co	60Ni	65Cu	75As	95Mo	101Ru	103Rh	105Pd	111Cd	189Os	193Ir	195Pt	202Hg	208Pb
Control	n.d.	0.06	0.20	0.67	n.d.	1.75	3.92	0.01	n.d.	0.00	1.00	1.46	0.05	0.07	0.06
Exposed to air	n.d.	0.08	0.25	0.66	n.d.	1.77	6.38	0.01	0.04	0.01	1.00	8.02	0.05	0.04	0.30

n.d. not detectable

CONCLUSION

The setup and operation of an elemental analysis laboratory for elemental impurities compliance should not be treated by pharmaceutical industry as a routine task. The requirements for lower detection limits and the frequent contamination from environment and lab apparatus make an elemental analysis lab distinct from other laboratories. Aside from the common clean lab practice such as tidy work area and exhaust ventilation, clean chemistry is also crucial for data quality including method accuracy, precision, and robustness. Lab cleanliness and lab practices aiming at contamination control should be emphasized when evaluating an elemental analysis laboratory for the quality of work it performed. Contamination control in an elemental analysis lab should not be treated slightly as simply rinsing flask several times. Extensive experience gained in environmental monitoring (12), food analysis (13), and other fields provides valuable resource for pharmaceutical industry in preparing for elemental impurities compliance.

It should be stressed that quality control samples should be analyzed along with the unknown sample as a means to monitor the presence and magnitude of contamination. Method blanks should be analyzed prior to unknown sample analysis. Elevated concentration above MDLs in method blank indicates contamination during sample preparation. The sample to be determined should be spiked with a known amount of analyte before sample preparation and be evaluated for its spike recovery. High recovery rate may indicate possible contamination from sample preparation. Lead is most subject to environment and lab apparatus contamination. Spike recovery for lead can be controlled below 130% if the clean lab practices suggested in this study are followed. It should be noted that method blanks and sample matrix-spiked quality control samples only provide clues of contamination from sample preparation and sample measurement. Contamination from sampling and sample storage should be carefully evaluated for sample integrity and sample container cleanliness. In general, an extractables study is required for evaluating container cleanliness.

Preparing vessels for elemental analysis requires acid soaking and thorough water rinsing. Demands for costly ultrapure acids and labor hours in vessel preparation may be alleviated by clean room facility such as a clean bench. While clean room is a luxury for elemental impurities analysis in pharmaceutical industry, a clean bench helps provide assurance of sample integrity in an elemental analysis lab. It is always desirable to prepare samples in a laminar flow environment where dust contamination can be minimized. Otherwise, significant cost on lab cleanliness control will occur. Controlling environmental contamination can be expensive. Some tips on environmental contamination control have been offered elsewhere (14). For high-throughput lab, it is cost-saving to use sub-boiling device to make in-house ultrapure acids.

All apparatus should be specified in the analytical method along with any cleaning procedure or special precaution with regard to sample integrity. Clean lab practices should be emphasized from the very beginning of method development. These practices aim at identifying and controlling critical process parameters that will impact method performance. Thus, the adoption of clean lab practice in an elemental analysis lab is compatible with the Quality by Design philosophy advocated by FDA for analytical method development.

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