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The Product Quality Research Institute elemental impurity interlaboratory study: Results and implications for industry☆

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ABSTRACT

Introduction: Pharmaceutical laboratories experienced a paradigm shift in drug product elemental impurity (EI) expectations in International Council on Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline Q3D and United States Pharmacopeia (USP) General Chapters <232>/<233>. These guidelines describe a risk-based approach to EI analysis. Few systematic evaluations of interlaboratory performance on EI analysis in pharmaceutics have been conducted following these guidelines. Our goal is to address key technical challenges faced by laboratories during the implementation of these regulations.
Materials and Methods: We organized an interlaboratory study using standardized samples and methodology to assess sample preparation and analysis variability. Participants performed microwave-assisted acid preparation of simulated pharmaceutical products and analyzed Class 1 and 2A EI's by inductively-coupled plasma-mass spectrometry (ICP-MS). Several laboratories performed X-ray Fluorescence spectroscopy (XRF) for comparison.
Results: ICP-MS reproducibility was high both within and between laboratories, except for Hg and V. Exhaustive extraction and total digestion were generally comparable, between 87 and 111 % for As, Cd, Co, and Pb. Total digestion exhibited lower variability than exhaustive extraction. Two types of microwave systems produced comparable results for most elements except Hg and Pb. The summation approach was comparable to direct analysis of tablets except for Hg and Cd, but summation demonstrated greater variability. XRF showed good agreement with ICP-MS and low replicate variability within labs.
Discussion and Conclusions: While the results were generally favorable, they demonstrate that some technical challenges remain to be addressed related to standardizing laboratory practices including interference correction strategies and selection of preparation methods. We discuss implications for method transfer between laboratories.

Introduction

Alongside the development of International Council on Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline Q3D, the United States Pharmacopeia (USP) published General Chapters ⟨232⟩ Elemental Impurities – Limits and ⟨233⟩ Elemental Impurities—Procedures [1,2], which outline a risk-based approach to product assessment and establish limits and compendial methods for trace metals in finished drug products. Following the release of the new guidelines, laboratory professionals and pharmaceutical industry stakeholders expressed an interest in gauging the progress of the analytical community in implementing the updated testing methods.

Pharmaceutical product elemental impurity (EI) assessment is an important area of exploration due to the broad need for these capabilities in the pharmaceutical industry. Following the implementation of the newly-harmonized USP <232>/<233> in 2018, all companies were required to develop risk assessments for filings of new products and

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eventually existing products for a list of 15 elements. Several acceptable options for the approach for risk assessment were provided, with the final decision on approach left largely up to the manufacturer, resulting in widespread discussion of the optimal approaches for determining the risk of certain elements. One approach involved analysis of raw materials to mitigate the need for testing of the finished product. However, this approach often necessitated the development of new methods for sample preparation and analysis by ICP-MS, as each sample matrix can have unique challenges associated with analysis. Furthermore, allowable daily exposure limits vary widely by element and by route of administration, resulting in limits of quantitation for some elements at quite low levels, especially when analyzing raw materials or excipients that may be used at widely differing proportions in different drug products. These nuances makes reliable analytical methods with minimal variability, and understanding the factors that produce variability, particularly important.

Even though development of pharmaceutical EI regulations was more than a decade in the making, as of the writing of this article, few scientific studies have been published on this topic in the context of the updated regulations. There have been reports investigating some EI's in herbal medicines based on ICH Q3D, studies which are important due to the documented potential for elemental contamination in herbal remedies, particularly in Ayurvedic herbal remedies [3–5]. One of these studies focused on an herbal ointment, a topic of particular interest due to the discussion around approaches for risk assessment of topical agents and the current limits established in the Second Supplement to USP 43 – PF 38 [1]. Reviews on the state of EI analysis in pharmaceutical products have periodically discussed analytical methods and trends in EI profiling [6,7].

An interlaboratory study was conducted in 2014 by the Coalition for the Rational Implementation of Elemental Impurity Guidelines Technical Analytical Challenges team using standardized evaluation samples and laboratory methods [8], which demonstrated high variability across labs using a standardized method. However, laboratories exhibited greater precision and accuracy when they were allowed to develop and use their own analytical methods. It also showed that analysis of standard samples by both ICP-MS and x-ray fluorescence (XRF) spectroscopy produced comparable results. On its completion, the study spurred additional discussion related to the materials analyzed, the methods used, and the number of participating laboratories. It was concluded that a second, more powerful, interlaboratory study could address some of these subjects in greater depth and follow up on the analytical community's readiness for routine determination of EI's in drug products. The second Interlaboratory Study was commissioned by the Product Quality Research Institute (PQRI) as a collaboration with volunteers from several non-profit research organizations, commercial pharmaceutical laboratories, government organizations, and universities.

Like the initial study, the primary objective of this work was to provide a data-driven way to address key technical challenges faced by pharmaceutical laboratories in preparation for implementation of EI regulations and explore the overall variability within labs and across labs. The specific study objectives were to perform an inter-laboratory data comparison for trace metal analysis of several standardized samples, evaluate the effectiveness of sample preparation by acid extraction and total digestion methods, compare the effectiveness of different types of microwave systems, examine the correlation between analysis of individual components of a drug product for the summation approach to final product analysis, and compare ICP-MS analysis of standard samples with XRF analysis. These studies are unique in their size, scope, comparison across sample preparation and analytical techniques, and in the statistical analysis that helps shed light on specific elemental ranges and conditions under which reliable measurements are achieved and where some common pitfalls in sample preparation or instrumental analysis may lie.

Materials and methods

We designed this study to address the above overarching objectives and further improve upon the methodology used in the 2014 interlaboratory study [8]. Specific adjustments that were made to the protocol included use of sample materials containing higher levels of EI's, evaluation of samples with multiple levels of EI's, and inclusion of pharmaceutically-sourced raw materials in the standardized samples where possible. Additional details are provided below.

Study initiation – laboratory recruitment

Laboratories were recruited from PQRI member organizations and other pharmaceutical analytical testing laboratories. Participants completed a questionnaire including the type of equipment available for sample preparation (microwave and otherwise) and analysis (primarily ICP-MS and XRF), as well as the laboratory's interest in contributing to optional aspects of the study (total digestion, summation of raw materials, and alternate instrumentation) [9]. In total, 28 ICP-MS and 5 XRF laboratories responded to the questionnaire, and 21 ICP-MS laboratories and 4 XRF laboratories returned results. Geographically, 13 labs were in North America, 11 labs were in Europe, and 1 lab was in Asia. A summary of laboratory equipment and practices is shown in Table 1. All laboratory equipment had undergone appropriate installation, operational, and performance qualification (IQ/OQ/PQ) procedures.

Design of the testing materials

Participating laboratories were asked to analyze tableted test materials containing "unknown" concentrations of the ICH Q3D Class 1 and 2A EI's [10]. In the current study, we limited focus on Class 1 elements (As, Cd, Hg, and Pb) and 2A elements (Co, Ni, V) as they were likely to be the most common elements addressed in risk assessments, due to their toxicity and (in the case of 2A) probability of occurrence. Tablets were produced containing EI's at three different levels that were comparable to the limits outlined in USP ⟨232⟩. The three levels were designed to mimic J, which is a function of the maximum permitted daily exposure (PDE) for an orally-administered drug, 30 % J, or the"control threshold" for EI's in an orally-administered drug product, and 300 % J, representing an elevated level of EI's in a drug product.

J is calculated by Eq. 1 as described in USP ⟨233⟩ for each element as [2]:

$$J = \frac{PDE\left(\frac{\mu g}{day}\right)}{Total\ Dilution\left(\frac{g\ component}{g\ product}\right) x\ Max\ Daily\ Use\left(\frac{g\ product}{day}\right)} \quad (1)$$

where the dilution factor represents the amount of a specific component in the formulation of a product and the maximum daily use of a product

Table 1
Final participant laboratory demographics (i.e., methods, microwave systems, etc.).

Total laboratories participating	25
ICP-MS laboratories	21 (84 %)
XRF Laboratories	4 (16 %)
ICP-MS Digestion methods	
Exhaustive extraction	19 (76 %)
Total digestion	7 (28 %)
Microwave systems (compared to ICP-MS labs above)	
SRC microwave	12 (55 %)
IPV microwave	10 (45 %)
Microwave Vessel materials	
Teflon	15 (68 %)
Quartz	7 (31 %)
Raw Materials analysis	13 (52 %)

is specified in g day^{-1}. We opted to use a hypothetical dosage of 1 g day^{-1} to ensure that our analytical concentrations would fall within the linear range of most current instrumentation to ensure that variability would not be influenced by values being too close to instrument detection limits. The design of the test materials will be described in a future manuscript [11], and so will not be discussed at length here. The final compositions of each raw material in all three concentration levels of test materials, and the concentration of all elemental impurities are shown in the Supplemental Information (Table S1, and S2, respectively).

Analytical method development

All test materials were provided to the Inorganic Analysis Laboratory at Procter and Gamble (reference laboratory), where two microwave assisted methods were developed and optimized [11]. Based on feedback from the participating laboratories, it was concluded that the uniform sample preparation method intended for use at all laboratories would be a moderately aggressive"exhaustive extraction" method utilizing HNO_3, and that an optional highly aggressive "total digestion" method would be available for use on a voluntary basis. For both methods, parameters were developed by the reference laboratory to accommodate both individually pressurized vessel (IPV) and single reaction chamber (SRC) microwave systems. During method development, the reference laboratory demonstrated that both exhaustive extraction and total digestion methods produced equivalent results for the sample tablets and raw materials. ICP-MS parameters were standardized as much as possible, with dilutions, gold stabilization, and quality control measures being fixed. Participants were given leeway to select collision cell gases and internal standards to minimize the need to purchase specialized consumables solely for this study. Standard written summaries of the methods were developed to ensure that all participants could follow the methods with minimal deviations. The methods are described here and full copies of the methods are available online for downloading [12,13].

ICP-MS analytical testing process workflow

Samples were shipped to participating laboratories based on their responses to the Participant Questionnaire. A standardized Reporting Template designed to minimize reporting variation and streamline data processing was provided to each laboratory by email. Information requested in the Reporting Template included manufacturer and model of laboratory equipment, reagent information (producer, lot number, and grade), analytical parameters used (collision cell gas, internal standards, etc.), and elemental concentrations for all materials tested.

All laboratories were asked to perform the exhaustive extraction method for the three tablet concentration levels at a minimum. Labs that agreed to participate in the optional summation approach analysis were asked to analyze the raw materials by the exhaustive extraction method. Labs that indicated they had appropriate facilities, instrumentation, and training were given the option to participate in the total digestion method comparison study.

ICP-MS standard sample preparation method – exhaustive extraction

Briefly, tablet and raw material samples were massed in triplicate into digestion vessels and 10 mL of ultra-trace metals grade concentrated HNO_3 (67–70 %) was added to each vessel with 50 μL of gold inorganic standard (1000 μg mL^{-1}). Triplicate method blank quality control samples were prepared to assess analyte background signal by only adding the acid and gold to vessels. Vessels were sealed and digested by microwave. Where possible, samples were digested by ramping to 175 °C over 10 min, then holding at a steady temperature for 10 min. Digests were allowed to cool in the microwave system to <60 °C, diluted to 50 mL with deionized (DI) water, and centrifuged or allowed to settle overnight before analysis. The digested sample was further diluted 50-fold by addition of concentrated HNO_3, ultra-trace metal grade HCl (34–37 %), and DI water to a final concentration of 2 % HNO_3 and 2 % HCl.

ICP-MS standard sample preparation method – total digestion

Fluoroboric acid solution was prepared by mixing 235 mL of ice-chilled ultra-trace metals grade hydrofluoric acid (HF, 47–51 %) and 100 g of ultra-trace metals grade boric acid slowly with stirring on ice [14]. Tablet and raw material samples were massed in triplicate into digestion vessels for preparation by microwave digestion. Subsequently, 0.5 mL of ultra-trace metal grade concentrated HCl, 2.5 mL of ultra-trace metal grade HNO_3, 0.5 mL of ultra-trace metal grade concentrated phosphoric acid (H_3PO_4, 80–90 %), and 1.0 mL of fluoroboric acid were added to each vessel. Samples were microwave digested by ramping up to the system's maximum safe temperature over 25 min, holding for 20 min, then allowing the digests to cool in the microwave system to <60 °C. The digests were diluted to a final volume of 50 mL with DI water, and then further diluted 50-fold by addition of concentrated HNO_3 and HCl and DI water to a final concentration of 2 % HNO_3, 2 % HCl, and 0.2 % HF.

Analysis instructions

Participants were instructed to start up and perform signal optimization and daily use checks per their individual manufacturer guidelines. Sample digests were analyzed by ICP-MS for arsenic (As), cadmium (Cd), mercury (Hg), lead (Pb), nickel (Ni), vanadium (V), and cobalt (Co) against an aqueous acid-matrix matched calibration curve consisting of five concentration levels across the span of expected instrumental concentrations and a solvent blank solution as shown in Table S3 (Supplemental Information). A linear, non-weighted regression curve was to be calculated for quantification of elements in samples. Results and limits of quantitation for all elements were calculated from the individual weight of each tablet or raw material and reported in units of ppm (μg g^{-1}). To standardize the results as much as possible while still allowing laboratories leeway to perform analysis without needing to order specialized supplies, analytical isotopes for the EI's were specified in the standard method as shown in Table S3, but laboratories could select their own internal standards and collision cell gases per their individual laboratory procedures. Most laboratories did not regularly use ammonia (NH_3) as a collision cell gas and so were allowed to use He as the collision cell gas for determination of V.

Acceptance criteria for quality control samples (initial calibrations, continuing calibration checks and blanks) were specified in the methods. Calibration curves would be considered acceptable if the correlation coefficient (R) of their linear least-squares regression was≥ 0.999, and calibration standards were acceptable if they were within 90–110 % of their target concentration (80–120 % at the lowest calibration standard). Continuing calibration check standards were analyzed every 10 samples and had to be within 80–120 % for all elements. Continuing calibration blank standards were also analyzed every 10 samples and could not exceed the lowest accepted calibration standard to be considered acceptable.

Special considerations for XRF analysis study

Typically, the XRF calibration methods for a specific drug product would be empirical in nature (i.e. the formulation composition would be consistent). However, since this study required significant variation to the formulation to achieve targeted Class I and IIa impurity levels, a standard empirical calibration would have been necessary for each formulation type/level which would be resource-prohibitive. Therefore, a Fundamental Parameters (FP) calibration approach was selected for this study [15–17]. This approach uses external addition of the EI's to several material compositions to develop a universal calibration method

across sample compositions. Although this approach requires additional preparation time, such calibration approaches are stable over very long periods of time without recalibration [18,19]. This approach is also designed to allow the instrument and data analysis software to account for a variety of sample compositions, which can impact the fluorescence signal detection, and account for situations where it is not possible to obtain materials that are completely free of the analytes (therefore making it impossible to prepare a true analytical"blank").

A unique silicon dioxide (SiO_2) material that had been pre-screened and found to contain no detectable EI's was used for standard preparation. Several levels of FP standards were prepared by spiking liquid standards to specified EI levels across the anticipated concentration range into powder mixtures containing the excipient materials at varying concentrations. Sample tablets were prepared by grinding, mixing, and pressing in a 35 mm die at a pressure of 20 tons for 1 minute. Prepared samples were analyzed on either a wavelength dispersive X-ray fluorescence (WDXRF) system, or an energy dispersive XRF (EDXRF) systems, depending on availability in each testing lab. Method performance was verified by reanalysis of two of the FP standard tablets as unknowns.

Statistical methods

Data were analyzed using the R software environment for statistical computing and graphics [20]. Before analysis, each laboratory was assigned a random ID number, and the file cross-referencing labs to ID numbers was kept separate from the analytical dataset for blinding purposes. All statistical computations (e.g., means, standard deviations, confidence intervals, repeatability, reproducibility, p-values) were performed on log-transformed concentrations, which were later transformed back to$\mu g\ g^{-1}$ for reporting and visualization. For calculating mean concentrations, values reported as below the limit of quantitation (LOQ) were set equal to the LOQ. For computing standard deviations, only values that were greater than the LOQ were included, to prevent underestimating variation in the data. To compute the relative contributions of within- and between-lab variance to overall variability, analysis of variance (ANOVA), with *t*- and F-tests were used to compare means and variances. The Shapiro-Wilk test was used to assess deviations from normality. Log-transformation and appropriate non-parametric tests (e.g., Wilcoxon, Kruskal-Wallis) were used to account for non-normality. Overall, no data were excluded from any of the analyses due to non-normality or extreme values.

Results

The full data set for reported concentrations are publicly available for further analysis [21]. Target LOQ's for each element in each material are shown in Table S4 and were computed using the lowest calibration standard concentration, the target mass of each raw material from the standard method or the average tablet mass (0.25 g), and the sample dilution factor from the method. Laboratories were requested to report values below LOQ as"less than LOQ", but several laboratories instead reported these numerical values. Prior to sample distribution, reference values for the evaluation samples were generated on subsamples of all three tablet levels by the method development laboratory. Method performance for participant labs was gauged by assessing analyte recovery and precision of results. The reference laboratory results are shown in Table S4.

Laboratory details

Although most laboratories used the internal standards and gases recommended in the standard method, some laboratories followed their internal protocols. The internal standard and collision cell gases used are shown in Table S5. Two labs used instruments without collision/reaction cells, and one indicated that they used correction equations for As and V. Two labs reported using a single internal standard for all analytes. Only one lab reported using NH_3 reaction cell gas for V. One ICP-MS laboratory altered the standard method so far that it was classified as a variable method, and as such it was excluded from analysis. Most laboratories followed the recommended method parameters, which suggests that internal standard selection played a minimal role in any observed variability between reported values and the reference laboratory and each other. While it is possible that the laboratories who did not report their internal standard elements may have used alternate elements, there were few such labs so it likely did not impact the findings.

The standard methods specified a temperature-controlled digestion method to be used for both types of microwave systems. Many microwave systems allow for either pressure/temperature control or power control depending on the age and configuration of the system. Several participant laboratories did not have systems allowing temperature controlled methods, necessitating slight adjustment of the method. We advised laboratories performing the total digestion to use the maximum safe operating temperature per manufacturer recommendations or internal safety protocols and record the temperature used in the reporting template. The reported digestion method parameters are shown in Table S6.

In the XRF laboratories, 3 of 4 used wavelength dispersive X-ray fluorescence (WDXRF) systems, which have higher sensitivity across more elements than energy dispersive XRF (EDXRF) systems [18,19]. All sample preparation variables varied to some degree (e.g., mixing times, oven temperatures, drying time, press loads, and press time). Count times on WD systems ranged from 30 to 360 s depending on the element and calibration range, with significantly longer count times for the EDXRF.

Comparison of measured values to reference values

We compared all reported concentrations to the reference values to determine whether there was a statistically significant difference for all laboratories, or for a subset of laboratories depending on the digestion method. We calculated the mean concentrations, standard deviation, and 95 % confidence intervals for all laboratories, all exhaustive extraction results, and all total digestion results. We calculated a p value for the reference value against that confidence interval. Comparisons to the reference laboratory results are summarized in Table 2 and shown in detail in Table S7.

While comparison for several analytes and materials were not possible because levels were below the limit of quantitation (e.g., lactose and starch), we can observe several trends. In tablets, Hg differed the most between the reference and participant laboratories, while Cd and V were also frequently significantly different. Hg consistently

Table 2
Comparison of participant ICP-MS results to reference results.

Material	All labs elements $p < 0.05$	Exhaustive extraction elements $p < 0.05$	Total digestion elements $p < 0.05$	Elements of Concern
Tablet Level 1	Hg, V	Hg, V	As, Cd, Co, Pb, V	Hg, V
Tablet Level 2	Cd, Co, Hg	Cd, Co, Hg	As, Co, Hg, V	Co, Hg
Tablet Level 3	Cd, Hg, V	Cd, Hg, V	Cd, Hg	Cd, Hg, V
Lactose				
Magnesium Aluminum Silicate	As, Ni	As, Ni	Ni, Pb	As, Ni
Red Ferric Oxide	As, Co, V	Co, Ni, V	Ni	Co, Ni, V
SiO_2 Standard (As, Co, Hg)	As, Co, Hg	As, Co, Hg	Hg	Co, Hg
SiO_2 Standard (Cd, Ni, Pb)	Ni	Hg, Ni		Ni
Starch				

demonstrated low recovery against the reference values (7.25 % - 26.3 % recovery). However, a similar loss of Hg was not observed in the SiO_2 XRF Standard Material that was the Hg source in tablets. These results suggest potential loss of Hg over time in prepared tablets.

Analysis of the raw materials demonstrated fewer differences, although it should be noted that the SiO_2 standards, which were the primary source for several elements, demonstrated several differences between the reference lab and participant labs. For the SiO_2 standards, laboratories performing the total digestion method demonstrated better agreement with the reference values than the exhaustive extraction laboratories, reflecting the relative difficulty of breaking down the SiO_2 material.

ICP-MS inter-laboratory repeatability and intra-laboratory reproducibility

Analysis of within (intra-) laboratory repeatability and between (inter-) laboratory reproducibility is summarized in Table 3 for tablets and Table 4 for raw materials and shown in detail in the Table S8 [22]. Tables S9 and S10 show summaries of the reproducibility results by digestion method for tablets and for raw materials, respectively, and Tables S11 and S12 show the detailed results. For all analytes and materials, the average reported concentration and the standard deviation and geometric coefficient of variation were calculated, both within labs (s_r, or"repeatability standard deviation") and between labs (s_R, or"reproducibility standard deviation"). The ratio of s_R:s_r was calculated as a measure of agreement between participant labs, where a ratio below 6 indicated agreement between labs. For almost all materials and elements, within-lab variability was lower than between-lab variability, demonstrating that laboratories' results were generally more internally consistent than when comparing across labs.

The ratio approach described above is similar to the concept of"robustness" as described in the USP. Robustness is defined in the context of an analytical validation as the ability of a method to withstand small changes to the method, often the instrument, the analytical day, or the analyst. Seeing as how the objective of the study was to measure the variability between labs, on different instruments, on different days, and often with small, intentional variations in the analytical approach, the analyses of reproducibility and repeatability could be seen as a measure of method robustness, although the purpose of the present study was not to validate the methods.

The false positive rate was calculated for all elements and materials as the number of laboratories reporting an element above the LOQ when none was expected to be present. V was the element that was erroneously reported most often. Visualizations of the comparison between participant laboratories and the reference laboratory for select elements are shown in Figs. 1 and S1-S2. Key comparisons are shown in Fig. 1 and in the Supplemental Information as box plots. Analysis of a liquid standard alongside the sample tablets demonstrated that although some variability in the reported elements can be attributed to instrumental variability, that factor alone cannot account for the observed variation.

Comparison of exhaustive extraction and total digestion

We compared results for all materials between exhaustive extraction and total digestion methods to assess the comparability of the two techniques. Results of the comparison are summarized in Table 5 and shown in detail in Table S13. Boxplots of select results are shown in Figures S3-S4. In our ANOVA analysis, a p-value below 0.05 indicated that the differences observed between the two values (e.g., the mean concentration of mercury reported from exhaustive extraction and total digestion, or SRC and IPV) were unlikely to have arisen by chance and are more likely to be a result of using different approaches. For many raw materials and elements, we could not calculate variability or compare methods because all or most of the reported values were below the LOQ. Only As and Hg exhibited significant differences in more than one material. In most cases where the within-lab standard deviation was significantly different between the two methods, the standard deviation for exhaustive extraction results was greater than that of total digestion.

Table 3
Summary of reproducibility for ICP-MS analysis of tablet test materials (all labs).

Material	Elemental recoveries vs Reference	Elements recovered 90–110 %	Highly reproducible elements (s_R:s_r < 6)
Tablet Level 1	21.1– 101 %	As, Cd, Co, Ni, Pb, V	As, Cd, Co, Hg, Ni, Pb, V
Tablet Level 2	10.7– 99.6 %	As, Cd, Co, Pb, V	As, Cd, Co, Hg, Ni, Pb, V
Tablet Level 3	7.48– 118 %	As, Cd, Co, Ni, Pb	As, Co, Ni, V

Comparison of microwave system types

Results of the comparison between elemental concentrations measured after digestion by SRC and IPV microwave systems are summarized in Table 5 and shown in detail in Table S14. Boxplots of select results are shown in Figures S5-S6. Only As, Hg, and Pb exhibited significant differences (p-values below 0.05) in more than one material. These results demonstrate that the mean concentrations for most elements are comparable between both types of systems, but that most elements did not have similar within- and between-lab variability when comparing the two types of systems. However, it is worth noting that in the case of microcrystalline cellulose, the mean concentration results were likely biased by data from a single laboratory.

Comparison of summation results to tablet analysis

Several laboratories analyzed raw materials to assess the comparability of the summation approach with direct analysis of EI's in drug products. We summed each lab's reported EI concentrations using the known formulation proportions of the raw materials (Table S2) in each tablet to calculate the summed elemental concentration. After calculating the summed values, we then compared them (a) to the lab-reported concentration of each tablet level and (b) to the reference value for each tablet level. Raw materials in which tablet concentrations were reported below the LOQ were excluded from the weighted sum. The comparison of summed results to the directly measured concentrations is summarized in Table 6 and shown in detail in Tables S15 and S16.

While several elements demonstrated strong agreement between the measured concentrations by direct analysis and by summation, there was less agreement of the within- and between-lab variability for the two approaches. As, Co, Ni, Pb, and V demonstrated good agreement for 2 of 3 concentration levels (V was only present in 2 tablet levels). In the case of Hg, the difference is a result of the analysis of the SiO_2 Standard (contributing As, Co, Hg), which demonstrated significantly better recovery of Hg than the tablets. In general, where significant differences were observed for the summed concentration and the directly measured concentration, a higher concentration was observed by summation than by direct analysis. For most elements, the within- and between-lab variability was significantly greater for the summation approach than for direct analysis. This may be a result of propagating errors throughout all raw materials or other factors in the analysis of the individual raw materials. As in the comparison to direct measurement, Ni and Pb demonstrated the closest agreement between the summed concentrations and reference values and Hg did not agree well with the reference values. Summation of As agreed well with reference values only for the total digestion method and Co and V only agreed well for exhaustive extraction. For As, Cd, Co, and Hg, the concentration determined by summation was greater than the reference value, and for Ni and Pb, the reference concentration was greater than the summed concentration.

Table 4
Summary of reproducibility for ICP-MS analysis of raw materials (all labs).

Material	False Positives (≥10 % of labs)*	Elemental recovery vs Reference	Elements recovered 90–110 %	Reproducible elements (s_R:s_r < 6)	Elements of Concern
Lactose	Ni, V	NA	NA	Ni, Pb	Ni, V
Magnesium Aluminum Silicate		99.4– 362 %	Pb, V	Co, Ni, Pb, V	As, Cd, Ni
Microcrystalline Cellulose	As, Cd, Co, Hg, Ni, V	NA	NA	Hg, Ni, Pb	As, Cd, Co, Hg, Ni, V
Red Ferric Oxide	Cd	83.0– 248 %	Ni	As, Co, Hg, Ni, Pb	Cd
SiO_2 Standard (As, Co, Hg)	Cd, Ni, Pb, V	88.7– 91.8 %	As	As, Co, Hg	V
SiO_2 Standard (Cd, Ni, Pb)	Co, Hg, V	33.0– 98.1 %	Cd, Ni, Pb	As, Cd, Ni, Pb	V
Starch	Ni, Pb, V	NA	NA		V
Stearic Acid	Cd, Pb, V	NA	NA		V

* A "false positive" was classified as a reported concentration of an analyte above the LOQ where no element was expected to be present from literature, CoA or other source.

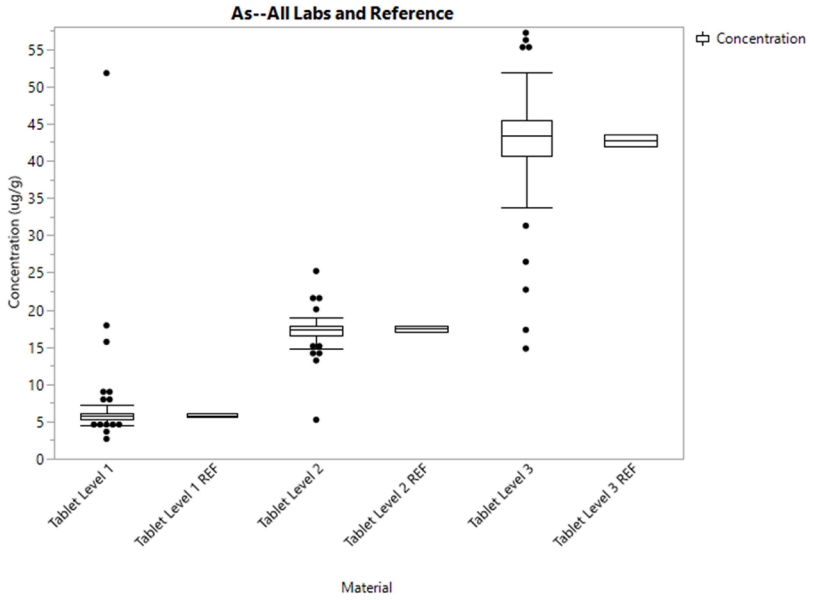

Fig. 1. Boxplot visualization of participant laboratory results for As in Sample Tablets compared to Reference laboratory results. Data points falling outside of the 95 % confidence interval are shown to indicate potential outliers.

XRF analysis study

Comparison of the measured concentration by ICP-MS and by XRF and of method variability are summarized in Tables 7–8 and shown in detail in Tables S17 – S20. Table 7 compares XRF results to reference values. As in the ICP-MS study, Hg demonstrated the most significant difference between the reference values and participant laboratories, with As and Cd also exhibiting significant differences. Hg also exhibited low recoveries against the reference values with high reproducibility in levels 1 and 2. Reported V concentrations by XRF were lower than those reported by ICP-MS and Cd concentrations were greater than those measured by ICP-MS, although this is primarily due to elevated results from a single laboratory. In Table S15, the results for all XRF laboratories are also compared to the expected concentrations calculated by summation of the raw materials [11].

Table 8 compares XRF to ICP-MS results, with additional detail shown in Tables S19-S20. Across all comparisons (all labs, exhaustive extraction, and total digestion), Cd concentrations reported by XRF were significantly, consistently higher than ICP-MS values. Also, Hg was consistently greater by XRF than by ICP-MS analysis, with statistically significant differences observed in the two lower tablet concentration levels.

Within-laboratory variability was consistently lower by XRF than by ICP-MS, and statistically significant differences in within-lab variability were observed for As, Ni, and V. Within-lab variability was lower by XRF analysis for As, Co, Ni, and V. A potential explanation for this observation may lie in how replicates were prepared in both studies. In the XRF labs, a single pellet was pressed for each concentration level from ground tablets and measured multiple times. In the ICP-MS analysis methods, replicates were prepared using separate tablets, and each digest was measured only once, an approach with inherent higher variability. Between-lab variability was generally lower for XRF than for ICP-MS analysis, although comparison of results obtained from total digestion with XRF results did not follow this trend due to lower between-lab variability by total digestion for most elements (Cd, Co, Ni, Pb, and V).

Although V replicability was better for ICP-MS than for XRF, the difference was only statistically significant for total digestion. For concentration levels where between-lab variability was low, it may be explained by the concentration level of the element compared to the calibration range for the element. Calibration concentrations were designed to be high enough to provide accuracy within reasonable count times on each element, so some low concentrations (e.g., Tablet Level 1) fell significantly below the lowest concentration of FP calibration standard for some elements, which would produce greater variability compared to elements within the calibration range. Future investigations should extend the calibration range of FP standards to account for lower concentration ranges.

Table 5
Summary of comparison of analytical methods analysis.

Test Material	Elements Average concentration $p < 0.05$	Within lab standard deviation $p < 0.05$	Between lab standard deviation $p < 0.05$	Elements of Concern
Exhaustive extraction vs total digestion				
Tablet Level 1	Hg	As, Cd, Co, Ni, Pb	Co	Hg
Tablet Level 2		As, Cd, Co, Hg, Ni, Pb, V	As, Co, Ni, V	
Tablet Level 3	As	As, Cd, Co, Hg, Ni, Pb, V	As, Cd, Co, Ni	As
Lactose	V			
Magnesium Aluminum Silicate		Pb	Pb	
Red Ferric Oxide	As, Ni			
SiO_2 Standard (As, Co, Hg)	Cd, Hg,			Hg
SiO_2 Standard (Cd, Ni, Pb)		Ni, Pb		
SRC vs IPV microwave digestion systems				
Tablet Level 1	Hg	As, Cd, Co, Hg, Pb, V	As	Hg
Tablet Level 2	Co, Hg, Pb	As, Ni, Pb	Cd, Co, Hg, Ni, Pb, V	Hg, Pb
Tablet Level 3	Hg, Pb, V	As, Co, Hg, Ni, Pb, V	As, Cd, Co, Hg, Ni, Pb	Hg, Pb
Magnesium Aluminum Silicate	Hg	As, Co, Ni, Pb, V	As, Cd, Co, Pb, V	
Microcrystalline Cellulose	*As, Co,* Hg, *Ni*			
Red Ferric Oxide	As	V		As
SiO_2 Standard (As, Co, Hg)	Hg, Pb	Co		Hg
SiO_2 Standard (Cd, Ni, Pb)		Ni		
Starch	V	V		

Note that sample matrices exhibiting no significant differences (e.g. stearic acid) were excluded from this table.

Table 6
Summary of analysis of the summation approach.

Material	Elements Average concentration $p <$ 0.05	Within lab standard deviation $p <$ 0.05	Between lab standard deviation $p <$ 0.05	Elements of Concern
Tablet Level 1	Hg, Pb	Cd, Co, Hg, V	Cd, Co, Hg, Pb, V	Hg
Tablet Level 2	Cd, Hg	As, Cd, Ni, V	As, Cd, Co, Pb	Cd
Tablet Level 3	As, Cd, Hg, V	Cd, Co, Hg, Pb, V	Co, Hg, Ni, Pb, V	Hg, V

Discussion

Analytical challenges and opportunities

In this study, our goal was to compare the results for standard samples from a range of laboratories to demonstrate analytical accuracy and precision between laboratories. In a search of recent literature (since 2021), almost all publications that have been produced in this area pertain to methods for measuring EI's in specific API's or specific products, making these comparisons particularly novel [23–25]. To demonstrate these two concepts, we grouped our comparisons in two ways: (1) comparing values by analyte and (2) comparing values by sample matrices. The method variables of interest may impact reproducibility and accuracy of results differently for a given test material or for an element depending on their characteristics (e.g., more recalcitrant materials may digest differently; Hg and As are volatile; different analytical interferences between elements). By systematically comparing results across laboratories, we can gain insight into the factors that can impact the agreement between laboratories.

Table 7
Comparison of XRF analysis laboratory results to reference values.

Material	Elemental recoveries vs Reference	Elements 90–110 % recovery vs Reference	Different Elements ($p < 0.05$)	Highly reproducible elements (s_R:s_r < 6)
Tablet Level 1	68.2– 129 %	As, Co	As, Cd, Hg	As, Cd, Hg, Pb
Tablet Level 2	24.2– 155 %	As, Co, Ni, Pb	Cd, Hg	As, Hg
Tablet Level 3	8.79– 145 %	Co, Pb	As, Cd, Hg	As

Table 8
Summary of comparison of ICP-MS analysis (all laboratories) to XRF analysis.

Material	Elements Average concentration $p < 0.05$	Within lab standard deviation $p < 0.05$	Between lab standard deviation $p < 0.05$
Tablet Level 1	Cd, Hg	As, Co, Ni, V	As, Co, Ni, V
Tablet Level 2	As, Cd, Hg	As, Co, Ni, Pb, V	Co
Tablet Level 3	As, Cd, Ni	As, Cd, Co, Ni,	As

In Table 9, elements are classified by how much their results differed between the participant labs and the reference values and on how reproducible the results were for an element. A similar table is presented for sample matrices in Figure S7 (Supplemental Information). Such an approach addresses both accuracy and precision and allows us to systematize the comparisons. The classifications in Table 9 are:

- "Strong Equivalence" indicates an analyte with high comparability between methods, high reproducibility within or between labs, or high accuracy against the reference value for most measurements (i.e., ≥60 %)

Table 9
Summary of comparisons of analytical results broken down by analyte.

	Strong Equivalence	Moderate Equivalence	Weak Equivalence
ICP-MS Results			
Reproducibility	As, Co, Ni	Cd, Hg, Pb	V
Exhaustive vs Total	Cd	As, Co, Hg, Ni, Pb	V
SRC vs IPV	Cd, Ni	As, Co, V	Hg, Pb
Summation Approach	Ni	As, Co, Pb	Cd, Hg, V
Comparison to Reference	Pb	As, Cd, Co, Ni	Hg, V
Overall ICP-MS	Ni	As, Cd, Co, Pb	Hg, V
XRF Results			
Reproducibility	As	Hg	Cd, Co, Ni, Pb, V
XRF vs ICP-MS (all)	Pb, V	Co, Hg, Ni	As, Cd
XRF vs ICP-MS (exhaustive)		Co, Hg, Ni, Pb, V	As, Cd
XRF vs ICP-MS (total)	Co, Pb	Hg, V	As, Cd, Ni
Comparison to Reference	Co, Ni, Pb, V		As, Cd, Hg
Overall XRF	Pb	Co, Ni, V, Hg	As, Cd

- "Moderate Equivalence" indicates an analyte with comparable performance between digestion methods or equipment OR comparable variability within and between laboratories, but not both, for most measurements (e.g., if an element demonstrated statistically similar measured concentrations between SRC and IPV systems, but demonstrated statistically significant differences for within- and between-lab variability, it would be classified as performing moderately)
- "Weak Equivalence" indicates an analyte that demonstrated low comparability between methods, low reproducibility within or between labs, or low accuracy against the reference value for most measurements.

For ICP-MS analysis, few elements were measured consistently between laboratories and between systems, as summarized in Table 9. The elements that consistently provided the most comparable results were Ni, As, Cd, Co, and Pb. For Hg and V, both elements have specific considerations that may play a role in their low comparability.

Analysis of vanadium

The most abundant isotope of V is 51 (99.75 % abundance), and in matrices containing high chloride content, the ClO^+ species can interfere with ICP-MS measurement. While polyatomic interferences are mostly resolved by using He or H_2/He collision cell gas, this approach cannot fully eliminate the interference at trace V levels. The appropriate gas for analysis of trace V in a Cl-containing sample matrix is NH_3 gas, which reacts with the interference and changes its molecular mass [26]. Since the standard methods included HCl, this interference likely impacted participant data quality. In the standard methods, we specified that NH_3 gas was recommended for analysis of V, however, only one participant laboratory used it, presumably due to its specialized nature and wide availability of other gases. The outcome here was that in tablet materials, the reported V concentrations were comparable to the reference laboratory, and the reproducibility was high for all 3 levels. However, in analysis of the raw materials, where only one material was known to contain significant concentrations of V, V exhibited the highest false positive rate likely due to the collision cell gases used.

Our results suggest that while NH_3 gas may not be necessary for analysis of final products where the daily exposure limit is high, it may be beneficial in situations where greater sensitivity is required, such as drug products for parenteral administration or inhalation where limits are significantly lower. This approach may also be important for analysis of raw materials like bulk excipients to ensure accurate concentrations for risk assessment. However, noting that the V PDE values in ICH Q3D and USP <232> are very high for oral administration (100 μg day^{-1}), it is uncommon that the element will play a role in oral administration products. It is also important to note that most elemental limits vary depending on the product administration route, so analytical variability is an important consideration for laboratories measuring at trace concentrations [1].

Mercury loss

Hg is traditionally measured by ICP-MS with either HCl or Au added to stabilize the element in solution. The standard method used here included Au, but we found that even in its presence, Hg recovery was low. This observation suggests that additional factors may be related to Hg stability in drug products. It is especially interesting that the Hg measured in the source SiO_2 reference material was not comparably low. Analysis of Hg in SiO_2 Standard (contributing As, Co, Hg) demonstrated 103 % recovery against the certified values (1080 μg g^{-1} expected, 1110 μg g^{-1} found), while analysis of Hg in the tablet samples exhibited 58.6 – 84.8 % recovery against expected values. Subsequent reanalysis of the SiO_2 standard demonstrated minimal change in the measured concentration over time (data not shown).

The primary Hg source in the tablet formulation was a SiO_2 reference material (Sigma Aldrich, XRF SiO_2 – High As, Co, Hg, Zn, product number MSH601; currently discontinued). This material was intended to mimic a geological source material with elevated Hg concentration and was selected due to limited availability of pharmaceutical excipients known to contain elevated Hg. Per the manufacturer CoA, the material was prepared using NIST SRM single-element solutions. Although our current hypothesis is that Hg volatilizes over time, additional experiments are needed to explore this explanation.

Raw material analysis

Materials that were known to contain EI's generally exhibited good reproducibility for elements >1.0 μg g^{-1}, particularly for Tablet levels 1 and 2 and the SiO_2 standards. However, analysis of the SiO_2 standards also exhibited high false positive rates for non-certified elements, which were not reflected in the reference laboratory data. Microcrystalline cellulose was the most challenging material, with the lowest reproducibility and highest false positive rate. Red ferric oxide, magnesium aluminum silicate, and the SiO_2 materials generally produced higher concentrations of the analytes by total digestion, likely because they represent more recalcitrant materials that can contain the elements of interest either in the lattice of the matrix or adsorbed to the material's surface.

Exhaustive extraction vs total digestion

Comparable concentrations were obtained for most analytes and materials from exhaustive extraction and total digestion, suggesting that the digestion method has a limited impact on the measured concentration of most analytes and materials in this study. The only notable exception was V, which likely suffered from the interferences discussed above. Most analytes demonstrated lower variability by total digestion than exhaustive extraction. This observation suggests that when EI's are present at low concentrations, the values measured by exhaustive extraction could exhibit greater uncertainty. It is possible that total digestion produces a more homogeneous digestion that lacks precipitate, which in turn produces less variability. This observation is consistent with the reproducibility analysis of the exhaustive extraction and total digestion results. Fewer analytes exhibited low reproducibility when prepared by total digestion (s_R:s_r > 6) than by exhaustive extraction.

These observations must be discussed in the appropriate context, as some may interpret them to mean that total digestion and exhaustive extraction are equivalent, making total digestion unnecessary. The appropriate interpretation is that the two digestion methods used on these materials, by these labs, produce comparable concentrations for most of the Class I and IIa elements. During method development, significant effort went into demonstrating that the two methods would produce comparable results [11]. Similarly, in real-world applications, it must be demonstrated that a total digestion method and an exhaustive extraction method are equivalent prior to pursuing exhaustive extraction for routine analysis. One such study that was published after the work for this report was already completed used such an approach for several API's and found that analyte recoveries between the two digestion approaches were generally comparable, but concluded that recoveries could vary depending on the residual carbon content of the digest and interference correction strategies employed [27]. Standardized criteria for establishing equivalency between total digestion and exhaustive extraction methods could benefit laboratories by providing clear guidelines for method development.

SRC vs IPV microwave systems

The measured elemental concentrations in materials where the analytes were known to be present was generally comparable between

SRC and IPV systems. However, for most materials (particularly the tablet materials) and elements, SRC systems produced lower variability, both within and between labs. The opposite was true for mineralogical materials like SiO_2 and ferric oxide. Our findings suggest that both types of systems will likely be suitable for most applications, especially for risk assessment purposes. It is unlikely that the increased variability produced by one type of microwave versus the other will impact measurement except where low detection limits are required (e.g., measuring EI's in bulk excipients).

XRF analysis comparisons

XRF results for some elements were comparable to ICP-MS, while others differed significantly from reference values and from the other participant laboratories. While the reproducibility analysis suggests that the results are not reproducible for any elements but As and Hg, this conclusion appears to be due to very low within-lab standard deviations for all elements. Comparing XRF results to ICP-MS laboratories performing either the exhaustive extraction method or the total digestion method indicated that neither extraction method performed better in comparison to XRF analysis. However, these conclusions may be a result of the low number of XRF laboratories participating in the study.

Summation of raw materials

The summation approach provides a mechanism for estimating elemental concentration of impurities in a final product as the weighted sum of the concentrations of all raw materials for the purpose of risk assessment. The equation to calculate the summed concentration of an EI is shown in (Eq. (2)) [1]:

$$Daily\ Dose\ PDE \geq \left[\sum M_1(C_M\ x\ W_M)\right]\ x\ D_D \quad (2)$$

where

M = each ingredient used to manufacture a dosage unit

C_M = element concentration in the component (μg g^{-1})

W_M = weight of the component in a dosage unit (g dosage $unit^{-1}$)

D_D = number of units in the maximum daily dosage (unit day^{-1})

This approach relies on accurate measurements of the elements in each component to predict the EI concentrations in the final product. We found mixed agreement between the summation approach and the direct analysis of tablets. As, Co, Ni, and V demonstrated the best agreement between the measured concentrations and the summed concentrations, although interlaboratory variability of the summation approach was generally greater than direct analysis, suggesting that this approach could particularly impact the analysis of trace impurities.

This aspect of the study, which measures EI's in all of the raw materials and then calculates the EI concentration in the final product based on the formulation proportions of all the ingredients, can indirectly address the topic of matrix effects in the tablet test materials, although a detailed assessment of matrix effects, as would be done during a formal method validation, was also outside the scope of the current study.

The study performed here provides insight into the variability of EI analysis methods, to inform method development efforts moving forward and to guide risk assessment efforts prior to regulatory submission. Our findings show that analysis of several elements in participant laboratories were comparable to the results obtained by the reference laboratory, indicating acceptable accuracy in the participant labs. Notable exceptions were cadmium, mercury and vanadium. Reproducibility was good for most analytes and was generally better for laboratories performing total digestion. Exhaustive extraction and total digestion were comparable for most analytes and materials, but total digestion was less variable. Comparison of SRC and IPV microwave systems was similar for most elements and materials present at appreciable concentrations, except mercury and lead. Greater variability was generally observed for IPV systems. Summation of EI's was comparable to direct analysis of tablets for most analytes but was more variable. XRF was comparable to ICP-MS for most analytes except As, Cd, and Hg and variability was lower by XRF.

Strengths and challenges

In designing this project, we implemented several improvements to the methodology compared to the 2014 interlaboratory study that strengthen the implications of the results. We have already touched on some of these in the Materials and Methods section, which include the use of pharmaceutically-relevant raw materials, EI concentrations that are a closer approximation to regulatory limits for Class 1 and 2A elements, the inclusion of more laboratories and laboratories that were located in Europe and Asia, and analysis of multiple levels of EI's rather than a single standard sample material.

However, there were some limitations that could be improved upon in the future that could further strengthen the results. Perhaps the most important limitation was the approaches that participant laboratories used for data reporting at the limit of quantitation. In a regulated pharmaceutical environment, it is a standard practice to not report analytical results below the limit of quantitation. However, for the purposes of comparison and determination of variability, especially for trace EI's, it could be more valuable to have the numerical values reported, which would allow for the statistical analysis to properly account for the trace concentrations reported, as well as more accurate data visualization. Additionally, one of the objectives of this study was to compare alternate instrumental approaches for measuring EI's. Although we included 4 XRF laboratories in the study, a more rigorous recruitment campaign for XRF laboratories and the inclusion of inductively-coupled plasma – optical emission spectroscopy (ICP-OES) could allow for a more robust assessment of the comparability of these instruments.

Conclusions

ICH Q3D and USP <232>/<233> represent a significant shift in analysis of EI's in drug products compared to historical wet chemistry methods. To ensure consistent data quality for regulatory oversight, we must understand factors contributing to analytical performance. Several variables play a role in analysis of EI's in pharmaceutical products, including preparation and analysis equipment and interference correction strategies. In our study, interlaboratory analysis of standard samples provided insight into the impacts of several of these factors on variability and accuracy, which can inform method development and risk assessment efforts during drug product lifecycles. Participant laboratories analyzed high priority elements and generated comparable results to the reference laboratory, indicating overall acceptable accuracy. Reproducibility was good for most analytes present at appreciable concentrations, both within and between laboratories. Although there were some challenging elements, notably Hg and V, participant labs generally performed consistently.

While the results are generally favorable and demonstrate more consistent performance across laboratories than the 2014 study, they also demonstrate that after implementation of USP <232>/<233>, some technical challenges still must be addressed related to standardizing laboratory practices and adoption of best practices related to interference correction strategies and method transfer between laboratories. While participant laboratories measured comparable concentrations for most analytes and materials, questions around the consistency of results between laboratories may be mitigated by addressing the above challenges.

Ethical statement

The work described herein does not include data collected from

human or animal subjects. All participant laboratory representatives have been informed of the outcomes of the research and the intent to publish deidentified aggregate data. All deidentified data has been made publicly available for review and additional analyses.

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CRediT authorship contribution statement

James M. Harrington: Writing – review & editing, Writing – original draft, Supervision, Project administration, Investigation, Funding acquisition, Data curation, Conceptualization. **Donna S. Seibert:** Writing – review & editing, Visualization, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Glenn Williams:** Writing – review & editing, Methodology, Investigation. **Thanh Nguyen:** Writing – review & editing, Methodology, Investigation. **Denise McClenathan:** Writing – review & editing, Validation, Methodology, Investigation, Conceptualization. **Stephen W. Erickson:** Writing – review & editing, Visualization, Formal analysis, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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