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Development and Validation of an Inductively Coupled Plasma Mass Spectrometry (ICP-MS) Method for Quantitative Analysis of Platinum in Plasma, Urine, and Tissues

Ti Zhang[1], **Shuang Cai**[1,2], **Wai Chee Forrest**[1], **Eva Mohr**[1,2], **Qiuhong Yang**[2], and **M. Laird Forrest**[1,2]

[1]HylaPharm LLC, Lawrence, USA

[2]Department of Pharmaceutical Chemistry, The University of Kansas, Lawrence, USA

Abstract

Cisplatin, a platinum chemotherapeutic, is one of the most commonly used chemotherapeutic agents for many solid tumors. In this work, we developed and validated an inductively coupled plasma mass spectrometry (ICP-MS) method for quantitative determination of platinum levels in rat urine, plasma, and tissue matrices including liver, brain, lungs, kidney, muscle, heart, spleen, bladder, and lymph nodes. The tissues were processed using a microwave accelerated reaction system (MARS) system prior to analysis on an Agilent 7500 ICP-MS. According to the Food and Drug Administration guidance for industry, bioanalytical validation parameters of the method, such as selectivity, accuracy, precision, recovery, and stability were evaluated in rat biological samples. Our data suggested that the method was selective for platinum without interferences caused by other presenting elements, and the lower limit of quantification was 0.5 ppb. The accuracy and precision of the method were within 15% variation and the recoveries of platinum for all tissue matrices examined were determined to be 85–115% of the theoretical values. The stability of the platinum-containing solutions, including calibration standards, stock solutions, and processed samples in rat biological matrices was investigated. Results indicated that the samples were stable after three cycles of freeze–thaw and for up to three months.

Keywords

Inductively coupled plasma mass spectrometry; ICP-MS; bioanalytical method validation; microwave digestion; biological matrices

Corresponding author: M. Laird Forrest, Department of Pharmaceutical Chemistry, University of Kansas, 2095 Constant Ave., Lawrence, KS 66047 USA. lforrest@ku.edu.

Conflict of Interest

SC, WCF, and MLF have a financial interest in HylaPharm LLC, which sponsored portions of this study.

Supplemental Material

All supplemental material mentioned in the text, consisting of recovery, stability and partial validation data is available in the online version of the journal, at http://asp.sagepub.com/supplemental.

Introduction

Advances in modern analytical techniques enabled detection and quantitation of trace-level elements in biological matrices, which simplified and expedited the analysis and pharmacokinetic investigations of metal-containing pharmaceuticals in experimental animal and human clinical studies. Platinum-containing chemotherapeutics, such as cisplatin, carboplatin, and oxaliplatin, are widely used worldwide in first-line therapies and as combination therapies in many cancers, including head and neck cancers, squamous cancer,[1–4] non-small cell lung cancer,[5–8] ovarian cancer,[9–11] and bladder cancers.[12–15] Although colorimetric assays for platinum analysis in biological matrices are still in use,[16] more robust, sensitive, and highly efficient instruments such as inductively coupled plasma mass spectrometry (ICP-MS),[17–20] atomic absorption spectroscopy (AAS),[21–25] and high-performance liquid chromatography (HPLC)[26–27] have become prevalent in the detection and quantitative analysis of trace-level platinum in biological matrices in the past decades. Besides the progress in the development of sensitive analytical detection methods, advances in the high throughput sample digestion techniques are also beneficial to researchers as they drastically reduce the time, labor, and resources involved for preparation of a large number of biological samples in a timely fashion. Conventional acid and heat treatments, as well as homogenization methods for tissue digestion, take hours of preparation time and multiple complex steps,[19,28,29] whereas a microwave-assisted digestion method shortens the length of time to less than 30 min.[27–30] For instance, the digestion method that we reported in this study requires merely 15 min.

Good laboratory practices (GLP) dictate that equipment and methods used in the production, manufacture, and analysis of chemical compounds shall be thoroughly tested to ensure that accurate and reliable data is obtained. This satisfies the regulatory requirements of 21 CFR 58, subpart D—Equipment and 21 CFR 211, subpart I—Laboratory Controls. Specifically, this procedure addresses “FDA Guidance for Industry—Bioanalytical Method Validation”. Thus, this validation protocol is designed to develop, establish, and validate a platinum analysis method for detecting platinum species in biological samples using ICP-MS.

This Food and Drug Administration (FDA) guidance applies to sponsors of investigational new drug applications (INDs). It provides instructions regarding bioanalytical procedures for quantitative determination of drugs and/or metabolites in biological matrices such as blood, plasma, plasma, urine, and tissue samples. This guidance contains recommendations for bioanalytical method validation, although the recommendations may be adjusted or modified depending on the specific type of analytical method used.

This validation of procedures for platinum analysis in biological samples using ICP-MS establishes documented evidence that the procedure is accurate, precise, selective, sensitive, reproducible, and stable for determining platinum contents in biological samples, including plasma, urine, and tissues. This validation is not only for ensuring the compliance of the regulatory requirements, but more importantly, for identifying and correcting the potential problems that could compromise the safety, pharmacokinetics, or efficacy of the investigational new drug.

Experimental

Materials

Platinum reference standard (1000 mg/L, lot number 19-194PTY) was purchased from Thomas Scientific (Swedesboro, NJ). Bismuth internal standard (10 μg/mL, lot number Y10030251-1R) and tuning solution containing ^{7}Li, ^{59}Co, ^{89}Y, ^{140}Ce, and ^{205}Tl (10 μg/L, lot number 408-0125-3) were purchased from Inorganic Ventures (Christianburg, VA). Trace metal grade concentrated nitric acid (67% wt) and trace metal grade concentrated hydrochloric acid (37% wt) were purchased from Fisher Scientific (Pittsburgh, PA). Water (≥18.2 MΩ) used in sample preparation was of trace metal grade and was produced by a Nanopure Infinity UV-UF water purification system.

Equipment

The Agilent Technologies 7500 series inductively coupled plasma mass spectrometry (ICP-MS), the Cetac ASX-520 autosampler, and the Neslab CFT-150 refrigerated recirculating chiller were installation, operationally and performance qualified (IQ/OQ/PQ) according to manufacturer and internal specifications by Pace Analytical Laboratories (Overland Park, KS). The ICP-MS system is equipped with a perfluoroalkoxy alkane standard (PFA-ST) nebulizer, a Scott type quartz spray chamber, a torch with a shield, a nickel sample cone, and a nickel shimmer cone. The ICP-MS is connected to a PC with a Windows XP operating system and controlled using Agilent ICP-MS ChemStation software (version B.04.00). Tissues were digested using a CEM Mars 5 Microwave Accelerated Reaction System (MARS) (Matthews, NC) with a set of 14 vessels. A control vessel is equipped with a fiber optic temperature sensor and a pressure sensor for regulating temperature and pressure via a user-defined digestion program.

ICP-MS method parameters

The integration time was 1 s for both platinum and bismuth. The analysis was repeated five times and the mean was calculated as the reported concentration of platinum. The total acquisition time was 32.5 s. The peristaltic pump program was optimized to improve the signal-to-noise ratio and the operating parameters are listed below. Before acquisition: sample uptake speed (0.40 revolutions per second (r/s), approximately 800 μL/min), uptake time (27 s), stabilization time (60 s); after acquisition rinse time: rinse speed (step 1: 0.40 r/s, step 2: 0.50 r/s, step 3: 0.30 r/s), rinse time (step 1: 70 s, step 2: 20 s, step 3: 100 s). During any rinse step, if platinum resulted in a count of less than 250 counts, the next rinse step would be skipped. Pt^{195} is used for platinum quantitation throughout the work unless otherwise noted. The operating conditions of the instrument are listed in Table 1.

Tissue digestion

One gram of rat liver, muscle, brain heart, kidney, and lung, and 100 mg of bladder, spleen, and lymph were pre-digested in 10 mL of concentrated nitric acid for 2 h prior to microwave digestion. The parameters of the microwaving cycle were as follows: power 1200 W; temperature, 200 °C; pressure, 200 psi; control style, ramp to temperature; hold time, 15 min; and stirring, off.

Sample preparation

All platinum standards and samples were prepared using the 1000 mg/L platinum reference standard. Samples matrices included 1% rat urine, 0.3% rat tissue digest, except for the bladder, spleen, and lymph node, which was 0.03% owing to the availability of the tissues. Bismuth was used as the internal standard for all assays.

Lower limit of quantitation

Samples containing platinum at concentrations of 0, 0.1, 0.2, 0.5, 1, and 2 parts per billion (ppb) were prepared in 1% urine and 0.3% liver digest. The instrument responses (counts) of platinum-containing samples were compared to the blank. The lowest platinum concentration that generated a response that was at least five times the response of the blank was determined as the lower limit of quantitation (LLOQ) for that matrix. LLOQs were separately determined for matrices of 1% urine and 0.3% liver digest samples.

Selectivity

Elements that may interfere with the quantitation of ^{195}Pt were screened. These elements include hafnium (^{179}Hf), molybdenum (^{97}Mo and ^{98}Mo), gadolinium (^{155}Gd and ^{158}Gd), terbium (^{155}Tb), and dysprosium (^{160}Dy), which may form HfO, MoMo, GdAr, GdCl, TbAr, and DyCl, respectively. Though elements such as oxygen (O), argon (Ar), and chlorine (Cl) may also be present and complexed with the aforementioned interfering metals, they were not tested due to their inevitable presence in the carrier gas, matrix, or rinse solution. A selectivity testing solution in 1% rat urine or 0.3% rat liver containing platinum at the LLOQ and at 10 times the LLOQ was prepared. Instrument responses (counts) of ^{179}Hf, ^{97}Mo/^{98}Mo, ^{155}Gd/^{158}Gd, ^{155}Tb, ^{160}Dy, and ^{195}Pt were recorded. Counts of ^{195}Pt must be greater than five times the counts of the individual interfering elements except for ^{97}Mo/^{98}Mo, which are known to be present in liver and kidneys/urine of rats. The acceptance criterion for Mo was that the counts for ^{97}Mo/^{98}Mo remained unchanged (90–110% of each other) between the 1×LLOQ and 10×LLOQ platinum solutions.

Calibration curve

A platinum calibration curve was generated using seven calibration standards in 1% rat urine and 0.3% rat liver digest, representing the biological fluids and tissue samples. The concentrations of the platinum calibration standards include 0, 0.5, 1, 5, 20, 40, and 50 ppb. Each sample was analyzed five times, and the average of the five replicates was calculated. Accuracy and precision in terms of relative standard deviation (%RSD) (SD/mean×100%) were determined. The acceptance criteria were as follows: RSD≤20% and accuracy within 80–120% of the true value for the 0.5 ppb standard; and RSD%≤15% and accuracy within 85–115% of the true value for 1, 5, 20, 40, and 50 ppb standards. In addition, a R^2 value≥0.995 was required.

Accuracy

The accuracy of the method was evaluated over the range of the calibration curve in both 1% rat urine and 0.3% rat liver digest. The accuracy of a low, medium, and high platinum concentration was determined using five measurements per concentration. The three

concentrations were 1, 25, and 45 ppb. The acceptance criteria were defined such that the accuracy was within 85–115% of the true value for all three standards.

Precision

The within-run and intra-batch precision was determined and evaluated over the range of the calibration curve in both 1% rat urine and 0.3% rat liver digest. The precision of a low, medium, and high platinum concentration was determined using five measurements per concentration. The three concentrations were 1, 25, and 45 ppb. Two analysts determined the intra-batch precision on two different days that consisted of four experiments: analyst A on days 1 and 2, analyst B on days 1 and 2. The acceptance criteria were defined such that the with-in run and intra-batch precision resulted in a %RSD of≤15% among five measurements for each concentration.

Recovery

The recovery experiment was performed by comparing the analytical results for platinum extracted from a matrix at three concentrations (low, medium, and high) with un-extracted standards that represent 100% recovery. The three concentrations were 1, 25, and 45 ppb. Known amounts of platinum were added into liver tissues and digested by MARS microwave. Digested samples were diluted and analyzed for platinum content by ICP-MS and compared to the true value of the concentration. The acceptance criteria for recovery were that the platinum content in the extracted samples was in the range of 85–115% of the un-extracted controls for the low, medium, and high concentrations.

Stability

The stability of platinum standards and samples were evaluated for the following stability tests, including (1) freeze and thaw stability, (2) short-term temperature stability, (3) long-term stability, (4) stock solution stability, (5) post-preparative stability, and (6) calibration standard stability. In the freeze and thaw stability experiments, three aliquots of low (1 ppb) and high (45 ppb) platinum quality control samples in 1% rat urine and 0.3% rat liver digest were stored at −80 °C for 24 h and thawed unassisted at room temperature. When completely thawed, the samples were refrozen for 24 h under the same conditions. The freeze–thaw cycle was repeated two more times and analyzed on the third cycle. The acceptance criteria for both low and high quality control samples after three cycles of freeze–thaw were within 15% of their true values. In the short-term temperature stability experiments, three aliquots of low (1 ppb) and high (45 ppb) platinum quality control samples in 1% rat urine and 0.3% rat liver digest were stored at room temperature for 24 h and analyzed. The acceptance criteria for both the low and high quality control samples after 24 h of storage at room temperature were within 15% of their true values. In the long-term stability experiments, three aliquots of low (1 ppb) and high (45 ppb) platinum quality control samples in 1% rat urine and 0.3% rat liver digest were prepared on day 1 and stored at −80 °C for up to three months. At months 1, 2, and 3, the samples were thawed unassisted at room temperature and analyzed. The results were compared to the true values of the quality control samples. Day 1 samples were also analyzed and reported as a control. The acceptance criteria for both low and high quality control samples after 1 -, 2 -, and 3-month storage at −80 °C were within 15% of their true values. In the stock solution stability

experiments, the stability of a 50 ppb platinum stock solution and a 50 ppb bismuth internal standard stock solution in 1% rat urine matrix were evaluated immediately after they were prepared and after 6 h of storage in the autosampler by recording and comparing the instrument responses between 0 and 6 h. The acceptance criteria were defined such that the accuracy of the 6 h result was within 15% variation of the 0 h result for both platinum and bismuth. In the post-preparative stability experiments, the stability of a 25 ppb quality control sample and an internal standard was assessed at the maximum duration of the anticipated runtime of 24 h and compared to the result at 0 h. The acceptance criteria were defined such that the accuracy of the 24 h result was within 15% variation of the 0 h result for both platinum and bismuth. Lastly, the stability of calibration standards in 1% rat urine containing 0, 0.5, 1, 5, 20, 40, and 50 ppb platinum were assessed on days 0, 1, 2, 3, 4, and 7. The acceptance criteria were that the accuracy was within 15% of their true values for all concentrations on the days tested except for the 0 and 0.5 ppb standards, which were allowed 20% variation compared to their true values.

Partial validation in other matrices

Partial validation was performed to transfer the method from 1% rat urine to other fluid matrices of a rat origin, such as plasma, and to transfer the method from 0.3% rat liver digest to other tissue matrices of a rat origin, such as brain, kidney, lungs, muscle, heart, spleen, bladder, and lymph nodes. A 1% rat plasma sample and 0.3% rat brain, lungs, kidney, muscle, and heart samples were used for the assay, whereas 0.03% rat spleen, bladder, and lymph node samples were used instead due to the small quantities available. In the partial validation experiment of 1% rat plasma, two sets of calibration standards were made, one of which was prepared in 1% rat plasma, and the other of which was prepared in 1% rat urine. Quality control samples containing 25 ppb platinum in 1% rat plasma were analyzed using both calibration curves. The accuracy and precision results were recorded. Similarly, in the partial validation experiment of rat tissue, two sets of calibration standards were made. One set was prepared in 0.3% of the specific rat tissue of validation except for spleen, bladder, and nodal tissues were prepared in 0.03% of tissue matrices. The other set of calibration standards were prepared in the same manner using 0.3% rat liver digest. Quality control samples containing 25 ppb platinum in 0.3% or 0.03% rat tissue were analyzed using both calibration curves. The accuracy and precision results were recorded. The acceptance criteria for all partial validation experiments in all biological matrices were that the accuracy of the quality control (QC) samples was within 15% of the true value and the precision of the QC samples were within 15% variation among the five replicates.

Results and discussion

The LLOQs of platinum were determined to be 0.5 ppb in both 1% rat urine and 0.3% rat liver matrices, which corresponded to greater than five times the response of a blank sample (Table 2). Selectivity of the instrument and the method was assessed in both 1% rat urine and 0.3% rat liver matrices by screening the potential interfering elements. Results indicated that the count of ^{195}Pt was greater than five times the counts of ^{179}Hf, ^{155}Gd/^{158}Gd, ^{155}Tb, and ^{160}Dy when platinum concentration equaled the LLOQ in both 1% rat urine and 0.3% rat liver. The counts of ^{97}Mo/^{98}Mo were not required to be less than five times the counts of

platinum due to the natural presence of the elements in rat liver and urine.[31] Thus, though platinum counts increased as platinum concentration increased by tenfold, the counts for $^{97}Mo/^{98}Mo$ remained similar, suggesting the presence of relatively constant quantity of Mo in rat matrices.

The linearity of platinum calibration curves in 1% rat urine and 0.3% rat liver digest met the acceptance criteria with a R^2 value greater than 0.995 (0.997 for 1% rat urine and 0.998 for 0.3% rat liver). The accuracy of the method was assessed by comparing three concentrations of the quality control samples in the range of the calibration curve with their true values in 1% rat urine and 0.3% rat liver matrices (Table 3). Results indicated that the accuracy of all levels of quality controls were within 15% of the true values. The within-run precision of the method was evaluated by comparing a low, medium, and high concentration quality control sample among five replicates in 1% rat urine and 0.3% rat liver matrices and was indicated by the relative standard deviation (%RSD) with an acceptance limit of 15%. The %RSD values for 1, 25, and 45 ppb QC samples were calculated to be 7.4%, 11.6%, and 12.8%, respectively, among five replicates in 1% rat urine. The %RSD values for 1, 25, and 45 ppb QC samples were calculated to be 1.0%, 13.7%, and 12.7%, respectively, among five replicates in 0.3% rat liver. Two analysts assessed the intra-batch precision on two different days. The result met the acceptance criteria with all %RSD values within 15% among five replicates (Table 4).

The recovery of the sample processing and preparation method was evaluated at a low, medium, and high quality control concentration. The amount of the extracted platinum after digestion by the acid treatment and microwaving was determined and compared to the theoretical value with 100% recovery. This result suggested that the recovery met the acceptance range of 85–115% of the theoretical values in 1% rat urine and 0.3% rat liver matrices (Supplemental Material, Table 5S). The result was consistent with similar methods in literature. Reifschneider et al. reported a recovery of 75–116% for platinum digested and extracted from mouse tissues using a MARS microwave system and analyzed by ICP-MS.[32] In addition to platinum, metals in marine species have been extracted and digested using a microwave system. For instance, Yang et al. reported recoveries of Na, Al, K, V, Co, Zn, Se, Sr, Ag, Cd, Ni, and Pb between 90–110% determined by ICP-MS.[33] In another microwave-assisted acid digestion procedure for determination of metal contents in marine invertebrates, recoveries of 85% and 110% were reported for Cu and Ba, respectively.[34]

Low (1 ppb) and high (45 ppb) platinum quality control samples were used for assessing the freeze–thaw, short-term stability, and long-term stability of the test samples in both rat urine and rat liver matrices. Results suggested that the samples were stable after three cycles of freeze–thaw and after short- and long-term storage for up to three months (Supplemental Material, Tables 6S–8S). Stock solutions of 50 ppb platinum and 50 ppb bismuth were stable in 1% rat urine for at least 6 h with a variation between 0 and 6 h within 15%. Platinum QC samples (25 ppb) and bismuth internal standard (50 ppb) were also stable in 1% rat urine for at least 24 h. Furthermore, the calibration standards prepared in 1% rat urine were determined to be stable at room temperature in the autosampler for at least seven days with accuracy within 85–115% compared to the day 0 result (Supplemental Material, Table 9S).

Thus, calibration standards may be reused for up to seven days as long as they are stored at the intended storage conditions.

After the completion of full method validation in two representative matrices of 1% rat urine and 0.3% rat liver digest, the method was partially validated in other rat matrices for method transfer purpose. These matrices include 1% rat plasma, 0.3% rat brain, lung, kidney, muscle, and heart, and 0.03% rat spleen, bladder, and lymph node. In Supplemental Material Table 10S, both QC1_plasma and QC2_plasma were a 25 ppb platinum QC sample prepared in 1% rat plasma. However, the calibration curves that were used to determine their concentrations were different. The concentration of QC1_plasma was determined using a calibration curve prepared in 1% plasma matrix, whereas the concentration of QC2_plasma was determined using a calibration curve prepared in 1% urine matrix. The accuracy and precision of both results met the acceptance criteria of within 15% variation. Because rat urine is more readily available than rat plasma, this validation experiment justified the use of a calibration curve prepared in rat urine matrix to determine the concentration of plasma platinum levels in unknowns. Similarly, liver is one of the major organs with larger quantity than other organs such as heart, spleen, and lymph nodes. Successful completion of method transfer from a validated method for Pt quantitation in a liver matrix to other matrices of a rat origin will enable us to determine Pt levels in organ using a calibration curve prepared in liver matrix. Results in Supplemental Material Table 10S suggested that the concentration of the 25 ppb QC sample in various organ matrices was determined accurately and precisely using a calibration curve made in 1% rat liver.

A sensitive, specific, and reliable ICP-MS method was developed and validated for quantitation of platinum in various rat tissue matrices such as urine, plasma, and digested tissues. The microwave-assisted digestion method was efficient and reproducible with good recovery of platinum. Bismuth was used as an internal standard throughout the development and validation. The method validation was performed according to the guidelines stated in the “FDA Guidance for Industry: Bioanalytical Method Validation”. In this work, comprehensive full validation was carried out for urine and liver matrices, representing a list of fluid and organ matrices that were also performed via partial validation and appropriate method transfer. The validation result suggested that the method has achieved a good agreement with the FDA guidance and has met the predetermined acceptance criteria for validation parameters including lower limit of quantitation, selectivity, calibration curve, accuracy, precision (within-run and intra-batch), recovery, and stability (freeze thaw, short-term, long-term, stock solution, post-preparative, and calibration standard).

We intended to develop and validate the aforementioned bioanalytical method to support regulator filings related to pharmaceutical compounds. Full validation of the method in the two representative rat matrices was critical as it enabled us to conduct efficient future method transfer according to FDA’s partial validation recommendations. The fully validated bioanalytical method may be transferred between laboratories and analysts, adapted to other matrix within species (e.g., rat urine to rat plasma) and other species within matrix (e.g., rat plasma to dog plasma) appropriate intra-assay determinations such as accuracy and precision comparisons. If future needs require a modified tissue processing procedure or a more sensitive ICP-MS equipment, the new methods may be partially validated by adapting and

transferring the current method, which favorably expedites the future drug development process.

Conclusions

We successfully developed and validated an ICP-MS method for quantitation of platinum in rat body fluids and tissues matrices. The validation was carried out according to the FDA bioanalytical method validation guidance for the pharmaceutical industry. The method has demonstrated appropriate selectivity, accuracy, precision, and stability for the intended purpose based on the FDA recommendations for IND sponsors. The microwave-assisted tissue digestion method also was shown to be efficient and reproducible with good recovery. The stability of the calibration standards, processed samples, and stock solutions were thoroughly investigated for their intended use at the proper storage conditions. The samples have been shown to be stable after three cycles of freeze/thaw and for up to three months at −80 °C, which is within the maximum intended storage and analysis duration.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

ICP-MS operating conditions.

ICP-MS tuning parameters	
Oxide ratio (156/140)	0.775%
Doubly charged (70/140)	1.485%
Plasma condition	
RF power	1200 W
RF matching	1.76 V
Sample depth	8 mm
Torch horizontal	0.8 mm
Torch vertical	0 mm
Carrier gas	1.02 L/min
Nebulizer pump	0.1 r/s
S/C temperature	2 °C
Ion lenses	
Extract 1	−101.2 V
Extract 2	−5 V
Einzel 1, 3	−100 V
Einzel 2	11 V
Omega bias	−40 V
Omega (+)	2.4 V
Omega (−)	−2 V
QP focus	2 V
Plate bias	−4.2 V
Q-pole parameters	
AMU gain	130
AMU offset	125
Axis gain	0.9998
QP bias	−8 V
Detector parameters	
Discriminator	8 mV
Analog HV	1740 V
Pulse HV	1200 V

S/C: spray chamber; AMU: atomic mass unit; QP: Q-pole; HV: high voltage.

Table 2

LLOQ determination in 1% rat urine and 0.3% rat liver digest.

Pt Conc, ppb	Response in counts (1% rat urine)	Response in counts (0.3% rat liver)
0	184	208
0.1	493	549
0.2	816	882
0.5	1841	1997
1	3510	3842
2	6886	7917

LLOQ: lower limit of quantitation.

Table 3

Accuracy test in 1% rat urine and 0.3% rat liver digest.

	1% rat urine		0.3% rat liver	
QC Conc, ppb	**Test result, ppb**	**Accuracy**	**Test result, ppb**	**Accuracy**
1	0.957	95.7%	1.053	105.3%
25	25.950	103.8%	24.700	98.8%
45	44.570	99.0%	46.090	102.4%

QC: quality control.

Table 4

Intra-batch precision test in 1% rat urine.

	Precision			
	Analyst A		Analyst B	
QC Conc, ppb	Day 1	Day 2	Day 1	Day 2
1	7.4%	3.4%	7.9%	0.7%
25	11.6%	1.3%	3.1%	3.5%
45	12.8%	8.3%	5.7%	1.1%