Appendix A6.1.3.31 Validation Summary ZZ36536-01 (3-HPMA/HBMA/CEMA in Urine)

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The following validation summary has been prepared by (b) (4) Full method validation reports and related SOPs are all available at (b) (4)

(b) (4)

Table 1. Validation Summary –3-HPMA in Urine - ZZ36536-01

Information Requested	Data
Validation Summary	(b) (4) Validation Study ZZ36536-01
Analyte	3-HPMA
Internal Standard (IS)	[$^{15}N^{13}C_3$]3-HPMA
Method Description	Solid phase extraction with analysis/detection by LC-MS/MS
Limit of Quantitation (ng/mL)	20.0 ng/mL
Average Recovery of Drug (% Mean)	54% at 60.0 ng/mL 64% at 5000 ng/mL
Average Recovery of IS (% Mean)	67% (human urine) 59% (UriSub®)
Standard Curve Concentrations (ng/mL)	20.0, 30.0, 60.0, 100, 200, 500, 1500, 3800, 4500, and 5000 ng/mL
QC Concentrations (ng/mL)	LLOQ QC, 60.0, 114, 296, 616, and 2470 ng/mL
QC Intra-Batch Precision Range (% CV)	1.2 to 10.0%
QC Intra-Batch Accuracy Range (% Bias)	-17.0 to 2.6%
QC Inter-Batch Precision Range (% CV)	2.9 to 10.2%
QC Inter-Batch Accuracy Range (% Bias)	-6.3 to -0.7%
Bench-Top Stability (Hrs)	Short-Term Stability: 24 hours in brown polypropylene tubes at ambient temperature under UV-shielded light Cumulative Short-Term Stability: 43 hours in brown polypropylene tubes at ambient temperature under UV-shielded light (total of all thaw cycles)
Stock Stability (Days)	Long-Term Stability for Stock Solutions (Stock): 277 days at approximately 500 µg/mL in methanol in polypropylene tubes at -20°C
Processed Stability (Hrs)	Post-Preparative Stability: 152 hours in a polypropylene 96 well plate at 5°C Processed Sample Integrity: 135 hours in a polypropylene 96 well plate at 5°C
Freeze-Thaw Stability (Cycles)	7 freeze (-20°C)-thaw (ambient temperature) cycles in brown polypropylene tubes under UV-shielded light

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Information Requested	Data
Long-Term Storage Stability (Days)	Long-Term Stability: 273 days (LLOQ QC), 651 days (low endogenous QC), 764 days (high QC), and 483 days (dilution QC) in brown polypropylene tubes at -20°C
Dilution Integrity	Up to 8070 ng/mL, diluted 5-fold
Selectivity	No significant interference at the retention time and mass transition of [$^{15}N^{13}C_3$]3-HPMA (IS) was observed from endogenous components in any of the 9 human urine lots screened

Additional Information –3-HPMA in Urine - ZZ36536-01			
Matrix		Human Urine	
Bioanalytical Method (BAM) SOP Number		BAM SOP ZZ36536-01	
Detector		AB SCIEX API 4000™	
Assay Volume Required		0.100 mL	
Regression Type		Weighted linear (1/concentration^2)	
Quantitation Method		Peak area ratio	
Multiple Analytes Measured by Assay		3-HPMA at 114 ng/mL fortified with HBMA at 5000 ng/mL and CEMA at 207 ng/mL	
Selectivity from Degradants or Isomers		2-HPMA (5000 ng/mL)	
Additional Selectivity Compound		N-Acety-S-(2-Carboxyethyl)-L-Cysteine (200 ng/mL)	
Quality Control Samples		Precision (% CV)	Accuracy (% Bias)
Inter-Batch	**LLOQ**	10.2	-5.5
	Low Spiking	5.3	-6.3
	Low Endogenous	3.1	-0.9
	Low-Medium	3.1	-0.7
	High-Medium	3.5	-1.1
	High	2.9	-0.8
Intra-Batch (Batch 50)[1] Aliquot Method: Manual Extraction Method: Automated	**LLOQ**	--	--
	Low Spiking	5.4	-5.5
	Low Endogenous	2.7	2.6
	Low-Medium	2.7	2.4
	High-Medium	2.8	1.9
	High	2.5	0.4
Intra-Batch (Batch 51) Aliquot Method: Manual Extraction Method: Automated	**LLOQ**	7.6	-1.0
	Low Spiking	2.8	-6.8
	Low Endogenous	1.9	-0.9
	Low-Medium	4.1	-0.7
	High-Medium	2.6	1.5
	High	3.4	1.2

[1] Batch fails intra-day PA, but passes batch acceptance criteria.

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Additional Information –3-HPMA in Urine - ZZ36536-01			
Intra-Batch (Batch 53) **Aliquot Method:** **Manual** **Extraction Method:** **Automated**	**LLOQ** **Low Spiking** **Low** **Endogenous** **Low-Medium** **High-Medium** **High**	3.9 9.7 2.6 1.2 3.5 1.5	-17.0 -6.3 -3.5 -2.0 -2.3 -1.2
Intra-Batch (Batch 52) **Aliquot Method:** **Manual** **Extraction Method:** **Automated**	**LLOQ** **Low Spiking** **Low** **Endogenous** **Low-Medium** **High-Medium** **High**	10.0 4.8 2.6 3.5 2.0 3.1	1.0 -7.3 0.0 -1.7 -3.4 -1.6
Intra-Batch (Batch 56) **Aliquot Method:** **Manual** **Extraction Method:** **Automated**	**LLOQ** **Low Spiking** **Low** **Endogenous** **Low-Medium** **High-Medium** **High**	5.4 1.8 1.9 1.9 1.6 2.1	-4.5 -5.5 -1.8 -1.4 -3.7 -3.2
Matrix Effect		No significant matrix effect was observed in 8 of the 9 human urine lots that were fortified with 3-HPMA near the concentration of the LLOQ (20.0 ng/mL), in any of the 9 human urine lots that were fortified near the concentration of the STD C (30.0 ng/mL), in 7 of the 9 human urine lots that were fortified near the concentration of the STD D (60.0 ng/mL), or in 8 of the 9 human urine lots that were fortified near the concentration of the STD E (100 ng/mL) samples	
Sample Shipping Stability		17 days in polypropylene tubes at -80°C	
Long-Term Stability for Stock Solutions (Substock)		146 days at 80.0 ng/mL in methanol in polypropylene tubes at -20°C	
Long-Term Stability for Stock Solutions (Internal Standard Stock)		Refer to long-term stability for stock solutions data collected from unlabeled 3-HPMA for labeled internal standard stability	
Long-Term Stability for Stock Solutions (Internal Standard Substock)		42 days at 4000 ng/mL in water in polypropylene tubes at -20°C	
Short-Term Stability for Stock Solutions (Stock)		6 hours at approximately 500 µg/mL in methanol in polypropylene tubes at ambient temperature under UV-shielded light	
Short-Term Stability for Stock Solutions (Substock)		6 hours at 80.0 ng/mL in methanol in polypropylene tubes at ambient temperature under UV-shielded light	
Short-Term Stability for Stock Solutions (Internal Standard Stock)		Refer to short-term stability for stock solutions data collected from unlabeled 3-HPMA for labeled internal standard stability	

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Additional Information –3-HPMA in Urine - ZZ36536-01	
Short-Term Stability for Stock Solutions (Internal Standard Substock)	6 hours at 4000 ng/mL in water in polypropylene tubes at ambient temperature under UV-shielded light
Stability of Analyte During Sample Collection and Handling	45 minutes in human urine in non-colored high-density polyethylene containers at ambient temperature under white light, followed by 24 hours in amber high-density polyethylene containers at 5°C in the absence of light, followed by 24 hours in polypropylene tubes at -20°C in the absence of light Up to 96 hours in smoker and non-smoker human urine in high-density polyethylene containers at 5°C, 20°C, and 40°C under UV-shielded light
Sample Aliquot Frozen Storage Stability	Samples aliquoted manually at a volume of 0.100 mL, stored for 92 hours in a polypropylene 96 well plate at -20°C prior to extraction
Batch Size	96 injections

Table 2. Validation Summary – HBMA in Urine - ZZ36536-01

Information Requested	Data
Validation Summary	(b) (4) Validation Study ZZ36536-01
Analyte	HBMA
Internal Standard (IS)	[$^{15}N^{13}C_3$]HBMA
Method Description	Solid phase extraction with analysis/detection by LC-MS/MS
Limit of Quantitation (ng/mL)	20.0 ng/mL
Average Recovery of Drug (% Mean)	76% at 60.0 ng/mL 83% at 5000 ng/mL
Average Recovery of IS (% Mean)	86% (human urine) 79% (UriSub®)
Standard Curve Concentrations (ng/mL)	20.0, 30.0, 60.0, 100, 200, 500, 1500, 3800, 4500, and 5000 ng/mL
QC Concentrations (ng/mL)	LLOQ QC, 60.0, 81.7, 265, 315, and 3710 ng/mL
QC Intra-Batch Precision Range (% CV)	1.6 to 11.2%
QC Intra-Batch Accuracy Range (% Bias)	-15.5 to 7.6%
QC Inter-Batch Precision Range (% CV)	2.8 to 7.6%
QC Inter-Batch Accuracy Range (% Bias)	-13.5 to 1.6%
Bench-Top Stability (Hrs)	Short-Term Stability: 24 hours in brown polypropylene tubes at ambient temperature under UV-shielded light Cumulative Short-Term Stability: 43 hours in brown polypropylene tubes at ambient temperature under UV-shielded light (total of all thaw cycles)
Stock Stability (Days)	Long-Term Stability for Stock Solutions (Stock): 426 days at approximately 500 µg/mL in methanol in polypropylene tubes at -20°C

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Information Requested	Data
Processed Stability (Hrs)	Post-Preparative Stability: 152 hours in a polypropylene 96 well plate at 5°C Processed Sample Integrity: 135 hours in a polypropylene 96 well plate at 5°C
Freeze-Thaw Stability (Cycles)	7 freeze (-20°C)-thaw (ambient temperature) cycles in brown polypropylene tubes under UV-shielded light
Long-Term Storage Stability (Days)	Long-Term Stability: 273 days (LLOQ QC), 651 days (low endogenous QC), 764 days (high QC), and 483 days (dilution QC) in brown polypropylene tubes at -20°C
Dilution Integrity	up to 5830 ng/mL, diluted 5-fold
Selectivity	No significant interference at the retention time and mass transition of [$^{15}N^{13}C_3$]HBMA (IS) was observed from endogenous components in any of the 9 human urine lots screened

Additional Information – 3-HPMA in Urine - ZZ36536-01			
Matrix		Human Urine	
Bioanalytical Method (BAM) SOP Number		BAM SOP ZZ36536-01	
Detector		AB SCIEX API 4000™	
Assay Volume Required		0.100 mL	
Regression Type		Weighted linear (1/concentration^2)	
Quantitation Method		Peak area ratio	
Multiple Analytes Measured by Assay		HBMA at 81.7 ng/mL fortified with 3-HPMA at 5000 ng/mL and CEMA at 207 ng/mL	
Selectivity from Degradants or Isomers		2-HPMA (5000 ng/mL)	
Additional Selectivity Compound		N-Acety-S-(2-Carboxyethyl)-L-Cysteine (200 ng/mL)	
Quality Control Samples		Precision (% CV)	Accuracy (% Bias)
Inter-Batch	**LLOQ** **Low Spiking** **Low Endogenous** **Low-Medium** **High-Medium** **High**	7.6 6.4 4.3 2.8 5.6 4.3	-13.5 -4.2 -0.2 0.0 1.6 -1.3
Intra-Batch (Batch 50)[2] **Aliquot Method: Manual** **Extraction Method: Automated**	**LLOQ** **Low Spiking** **Low Endogenous** **Low-Medium** **High-Medium** **High**	-- 3.9 2.9 2.1 5.9 4.1	-- -4.2 -1.7 0.4 1.0 0.3

[2] Batch fails intra-day PA, but passes batch acceptance criteria.

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Additional Information – 3-HPMA in Urine - ZZ36536-01			
Intra-Batch (Batch 51) **Aliquot Method:** **Manual** **Extraction Method:** **Automated**	**LLOQ** **Low Spiking** **Low** **Endogenous** **Low-Medium** **High-Medium** **High**	6.9 4.2 5.1 3.0 4.4 2.5	-13.0 -5.2 2.4 0.4 3.5 0.5
Intra-Batch (Batch 53) **Aliquot Method:** **Manual** **Extraction Method:** **Automated**	**LLOQ** **Low Spiking** **Low** **Endogenous** **Low-Medium** **High-Medium** **High**	8.2 11.2 5.9 2.8 3.9 1.6	-10.5 -6.0 -0.1 0.4 7.6 -2.7
Intra-Batch (Batch 52) **Aliquot Method:** **Manual** **Extraction Method:** **Automated**	**LLOQ** **Low Spiking** **Low** **Endogenous** **Low-Medium** **High-Medium** **High**	9.6 3.1 3.4 3.2 3.4 7.5	-15.5 -6.7 -0.6 -1.1 -4.1 -0.5
Intra-Batch (Batch 56) **Aliquot Method:** **Manual** **Extraction Method:** **Automated**	**LLOQ** **Low Spiking** **Low** **Endogenous** **Low-Medium** **High-Medium** **High**	6.0 3.8 3.6 3.4 3.7 1.9	-14.0 1.7 -1.1 1.1 0.3 -3.8
Matrix Effect		No significant matrix effect was observed in 6 of the 9 human urine lots that were fortified with HBMA near the concentration of the LLOQ (20.0 ng/mL), in 8 of the 9 human urine lots that were fortified near the concentration of the STD C (30.0 ng/mL), in 7 of the 9 human urine lots that were fortified near the concentration of the STD D (60.0 ng/mL), or in 8 of the 9 human urine lots that were fortified near the concentration of the STD E (100 ng/mL) samples	
Sample Shipping Stability		17 days in polypropylene tubes at -80°C	
Long-Term Stability for Stock Solutions (Substock)		146 days at 80.0 ng/mL in methanol in polypropylene tubes at -20°C	
Long-Term Stability for Stock Solutions (Internal Standard Stock)		refer to long-term stability for stock solutions data collected from unlabeled HBMA for labeled internal standard stability	
Long-Term Stability for Stock Solutions (Internal Standard Substock)		42 days at 2000 ng/mL in water in polypropylene tubes at -20°C	
Short-Term Stability for Stock Solutions (Stock)		6 hours at approximately 500 µg/mL in methanol in polypropylene tubes at ambient temperature under UV-shielded light	

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Additional Information – 3-HPMA in Urine - ZZ36536-01	
Short-Term Stability for Stock Solutions (Substock)	6 hours at 80.0 ng/mL in methanol in polypropylene tubes at ambient temperature under UV-shielded light
Short-Term Stability for Stock Solutions (Internal Standard Stock)	refer to short-term stability for stock solutions data collected from unlabeled HBMA for labeled internal standard stability
Short-Term Stability for Stock Solutions (Internal Standard Substock)	6 hours at 2000 ng/mL in water in polypropylene tubes at ambient temperature under UV-shielded light
Stability of Analyte During Sample Collection and Handling	45 minutes in human urine in non-colored high-density polyethylene containers at ambient temperature under white light, followed by 24 hours in amber high-density polyethylene containers at 5°C in the absence of light, followed by 24 hours in polypropylene tubes at -20°C in the absence of light Up to 96 hours in smoker and non-smoker human urine in high-density polyethylene containers at 5°C and 20°C under UV-shielded light and up to 48 hours in smoker and non-smoker human urine in high-density polyethylene containers at 40°C under UV-shielded light
Sample Aliquot Frozen Storage Stability	Samples aliquoted manually at a volume of 0.100 mL, stored for 92 hours in a polypropylene 96 well plate at -20°C prior to extraction
Batch Size	96 injections

Table 3. Validation Summary – CEMA in Urine - ZZ36536-01

Information Requested	Data
Validation Summary	(b) (4) Validation Study ZZ36536-01
Analyte	CEMA
Internal Standard (IS)	[$^{15}N^{13}C_3$]CEMA
Method Description	Solid phase extraction with analysis/detection by LC-MS/MS
Limit of Quantitation (ng/mL)	0.275 ng/mL
Average Recovery of Drug (% Mean)	86% at 0.828 ng/mL 82% at 207 ng/mL
Average Recovery of IS (% Mean)	85% (human urine) 84% (UriSub®)
Standard Curve Concentrations (ng/mL)	0.275, 0.415, 0.828, 2.75, 6.90, 20.7, 41.5, 104, 186, and 207 ng/mL
QC Concentrations (ng/mL)	LLOQ QC, 0.689, 0.828, 3.50, 60.7, and 162 ng/mL
QC Intra-Batch Precision Range (% CV)	1.4 to 7.5%
QC Intra-Batch Accuracy Range (% Bias)	-12.7 to 5.1%
QC Inter-Batch Precision Range (% CV)	3.8 to 10.0%
QC Inter-Batch Accuracy Range (% Bias)	-4.4 to 0.6%

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Information Requested	Data
Bench-Top Stability (Hrs)	Short-Term Stability: 24 hours in brown polypropylene tubes at ambient temperature under UV-shielded light Cumulative Short-Term Stability: 43 hours in brown polypropylene tubes at ambient temperature under UV-shielded light (total of all thaw cycles)
Stock Stability (Days)	Long-Term Stability for Stock Solutions (Stock): 276 days at approximately 138 µg/mL in methanol in polypropylene tubes at -20°C
Processed Stability (Hrs)	Post-Preparative Stability: 152 hours in a polypropylene 96 well plate at 5°C Processed Sample Integrity: 135 hours in a polypropylene 96 well plate at 5°C
Freeze-Thaw Stability (Cycles)	7 freeze (-20°C)-thaw (ambient temperature) cycles in brown polypropylene tubes under UV-shielded light
Long-Term Storage Stability (Days)	Long-Term Stability: 273 days (LLOQ QC), 651 days (low endogenous QC), 764 days (high QC), and 483 days (dilution QC) in brown polypropylene tubes at -20°C
Dilution Integrity	Up to 667 ng/mL, diluted 5-fold
Selectivity	No significant interference at the retention time and mass transition of [$^{15}N^{13}C_3$]CEMA (IS) was observed from endogenous components in any of the 9 human urine lots screened

Additional Information – CEMA in Urine - ZZ36536-01			
Matrix		Human Urine	
Bioanalytical Method (BAM) SOP Number		BAM SOP ZZ36536-01	
Detector		AB SCIEX API 4000™	
Assay Volume Required		0.100 mL	
Regression Type		Weighted linear (1/concentration^2)	
Quantitation Method		Peak area ratio	
Multiple Analytes Measured by Assay		CEMA at 0.689 ng/mL fortified with 3-HPMA at 5000 ng/mL and HBMA at 5000 ng/mL	
Selectivity from Degradants or Isomers		2-HPMA (5000 ng/mL)	
Additional Selectivity Compound		N-Acety-S-(2-Carboxyethyl)-L-Cysteine (200 ng/mL)	
Quality Control Samples		Precision (% CV)	Accuracy (% Bias)
Inter-Batch	**LLOQ**	10.0	-4.4
	Low Endogenous	4.6	-1.2
	Low Spiking	5.7	0.6
	Low-Medium	3.8	-1.1
	High-Medium	4.1	-1.8
	High	4.9	-1.9

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Additional Information – CEMA in Urine - ZZ36536-01

Intra-Batch (Batch 50)[3] **Aliquot Method: Manual** **Extraction Method: Automated**	**LLOQ**	--	--
	Low Endogenous	3.4	0.0
	Low Spiking	6.0	-1.8
	Low-Medium	2.5	0.3
	High-Medium	1.9	2.6
	High	3.7	0.6
Intra-Batch (Batch 51) **Aliquot Method: Manual** **Extraction Method: Automated**	**LLOQ**	7.7	3.3
	Low Endogenous	5.5	-0.3
	Low Spiking	4.2	5.1
	Low-Medium	4.4	-0.3
	High-Medium	2.2	-0.7
	High	2.1	1.9
Intra-Batch (Batch 52) **Aliquot Method: Manual** **Extraction Method: Automated**	**LLOQ**	7.0	-3.3
	Low Endogenous	3.5	0.6
	Low Spiking	6.5	0.5
	Low-Medium	4.6	-0.3
	High-Medium	1.7	-2.0
	High	2.8	-1.2
Intra-Batch (Batch 56) **Aliquot Method: Manual** **Extraction Method: Automated**	**LLOQ**	7.5	-12.7
	Low Endogenous	4.7	-4.9
	Low Spiking	4.5	-1.2
	Low-Medium	1.3	-4.3
	High-Medium	2.4	-6.9
	High	1.4	-8.6

Matrix Effect	No significant matrix effect was observed in any of the 9 human urine lots that were fortified with CEMA near the concentration of the LLOQ (0.200 ng/mL), in any of the 9 human urine lots that were fortified near the concentration of the STD C (0.300 ng/mL), in 7 of the 9 human urine lots that were fortified near the concentration of the STD D (0.600 ng/mL), or in 8 of the 9 human urine lots that were fortified near the concentration of the STD E (2.00 ng/mL) samples
Sample Shipping Stability	17 days in polypropylene tubes at -80°C
Long-Term Stability for Stock Solutions (Substock)	127 days at 1.10 ng/mL in methanol in polypropylene tubes at -20°C
Long-Term Stability for Stock Solutions (Internal Standard Stock)	Refer to long-term stability for stock solutions data collected from unlabeled CEMA for labeled internal standard stability
Long-Term Stability for Stock Solutions (Internal Standard Substock)	72 days at 15.0 ng/mL in water in polypropylene tubes at -20°C
Short-Term Stability for Stock Solutions (Stock)	6 hours at approximately 138 µg/mL in methanol in polypropylene tubes at ambient temperature under UV-shielded light

[3] Batch fails intra-day PA, but passes batch acceptance criteria.

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Additional Information – CEMA in Urine - ZZ36536-01	
Short-Term Stability for Stock Solutions (Substock)	6 hours at 1.10 ng/mL in methanol in polypropylene tubes at ambient temperature under UV-shielded light
Short-Term Stability for Stock Solutions (Internal Standard Stock)	Refer to short-term stability for stock solutions data collected from unlabeled CEMA for labeled internal standard stability
Short-Term Stability for Stock Solutions (Internal Standard Substock)	6 hours at 15.0 ng/mL in ultrapure water in polypropylene tubes at ambient temperature under UV-shielded light
Stability of Analyte During Sample Collection and Handling	45 minutes in human urine in non-colored high-density polyethylene containers at ambient temperature under white light, followed by 24 hours in amber high-density polyethylene containers at 5°C in the absence of light, followed by 24 hours in polypropylene tubes at -20°C in the absence of light Up to 96 hours in smoker and non-smoker human urine in high-density polyethylene containers at 5°C, 20°C, and 40°C under UV-shielded light
Sample Aliquot Frozen Storage Stability	Samples aliquoted manually at a volume of 0.100 mL, stored for 92 hours in a polypropylene 96 well plate at -20°C prior to extraction
Batch Size	96 injections

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