

Table S1. The concentration of digoxin (ng/ml) in blood serum, urine and amniotic fluid at the observation points depending on the genotyping data of the pregnant woman according to ABCB1.

Groups of study, ng/ml	CC	Allele T	p-value
1st point			
Digoxin in blood*	1.5±0.5	1.7±0.6	0.583
Digoxin in urine**	459 (320;665)	579 (382,743)	0.354
Digoxin in amniotic fluid**	2.3 (1.9;2.6)	2.3 (1.3;3.5)	0.844
2nd point			
Digoxin in blood**	1.7 (1.2; 1.7)	1.8 (1.5; 2)	0.159
Digoxin in urine*	600±200	700±300	0.448
Digoxin in amniotic fluid*	2.1±0.8	4±2	0.127
3rd point			
Digoxin in blood*	1.9±0.3	1.8±0.5	0.681
Digoxine in urine*	900±200	600±400	0.12
4th point (Delivery)			
Digoxine in blood*	1.0±0.5	1.1±0.8	0.733
Digoxin in urine*	500±500	300±200	0.203
Digoxin in amniotic blood*	4.1±0.3	4±2	0.86
Digoxin in newborn blood*	0.4±0.2	0.5±0.4	0.265
*The data presented as M±SD (95% c.i.), variance analysis.			
**The data presented as Me(Q1;Q3), Mann-Withey criteria			

Table S2. Intra- and interday precision and accuracy HPLC-MS/MS experiments (three different days) at four digoxin/sotalol concentrations (LOQ, low QC, medium QC, and high QC) in plasma, urine and amniotic fluid.

Analyte	Matrix	QC, type	QC, concentration, ng/ml (digoxin) and µg/ml (sotalol)	Intraday precision (RSD, %, n=5)			Intraday accuracy (%, n=5)			Interday precision (RSD, %,1)	Interday accuracy (%, n=3)
				1 day	2 day	3 day	1 day	2 day	3 day		
Digoxin	Plasma	LOQ	0.6	3.7 6	2.2 4	1.8 0	- 8.2 2	- 11. 15	- 12. 90	3.10	-10.80
		low QC	1.8	7.9 4	6.4 7	4.2 5	5.3 2	- 3.3 8	- 11. 43	9.10	-3.20
		medium QC	5.0	1.0 0	2.8 9	6.3 0	- 14. 06	- 10. 72	- 9.0 7	4.20	-11.30

		high QC	7.5	7.9 1	1.9 3	9.7 5	1.6 5	- 12. 90	1.0 1	9.60	-3.40
Sotalol	Plasma	LOQ	0.2	2.9 8	1.0 7	14. 40	15. 33	18. 43	0.6 2	12.00	11.50
		low QC	0.6	9.3 0	5.3 8	2.9 3	3.8 1	6.3 9	12. 41	10.40	-0.70
		medium QC	5.0	10. 65	2.2 0	3.0 3	6.6 9	11. 52	11. 40	12.10	2.30
		high QC	7.5	5.9 0	5.6 8	10. 12	5.7 4	4.3 5	- 6.1 4	8.90	1.30
Digoxin	Urine	LOQ	10.0	0.2 4	1.7 2	1.3 4	14. 12	12. 74	11. 89	12.60	4.50
		low QC	25.0	10. 72	12. 16	8.7 1	7.4 2	1.6 2	6.3 2	10.90	0.00
		medium QC	200.0	6.6 9	8.5 2	8.1 1	4.5 9	- 2.7 0	- 8.4 5	7.90	-3.10
		high QC	500.0	10. 25	6.7 8	6.5 1	6.6 9	- 4.5 2	- 6.8 7	9.60	-1.60
Sotalol	Urine	LOQ	10.0	2.0 3	5.5 5	7.6 6	13. 20	- 5.5 2	- 2.7 1	6.70	-7.10
		low QC	30.0	1.3 8	2.1 3	8.4 0	13. 41	- 13. 21	- 4.7 1	12.30	-1.50
		medium QC	500.0	1.2 4	5.3 9	7.2 5	12. 52	- 0.6 8	- 6.8 9	7.70	6.20
		high QC	750.0	3.2 1	2.2 2	9.4 7	12. 09	10. 46	- 1.5 9	8.70	7.00
Digoxin	Amniotic fluid	LOQ	0.5	4.6 3	4.9 9	2.1 5	5.1 5	- 5.4 4	- 12. 70	8.20	-4.30
		low QC	1.5	7.6 7	7.0 5	11. 66	7.0 5	- 6.3 7	- 1.5 2	9.20	-4.00
		medium QC	5.0	4.6 8	6.8 9	10. 60	9.1 6	- 7.6 7	- 0.3 9	8.30	-5.50
		high QC	7.5	2.4 6	4.5 0	8.3 4	12. 81	- 9.1 8	- 1.5 5	7.90	-6.80

Sotalol	Amniotic fluid	LOQ	0.2	13.33	11.21	8.35	6.65	0.68	7.10	11.90	-0.10
		low QC	0.6	5.67	10.14	6.92	10.59	6.71	5.18	7.70	7.50
		medium QC	5.0	7.77	4.17	11.21	7.75	6.47	4.33	9.60	3.30
		high QC	7.5	5.40	3.77	4.85	10.29	6.81	6.54	4.80	7.90

Table S3. Matrix effect and extraction recovery results for three QC levels (LOQ, medium QC, and high QC).

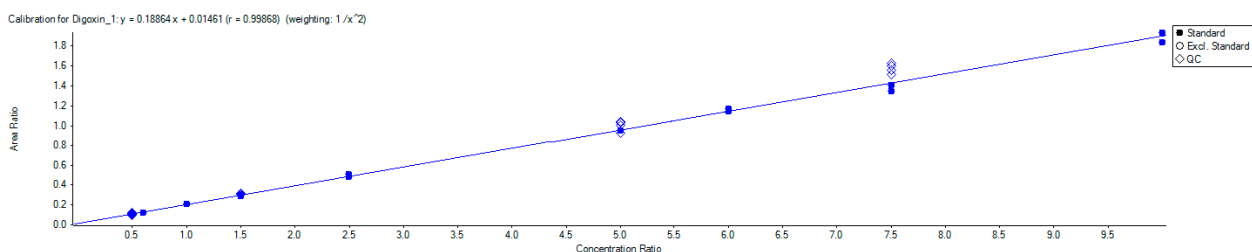
Analyte	Matrix	Matrix effect (ME, n=3), %			Recovery (ME, n=3), %		
		LLOQ	Medium QC	High QC	LLOQ	Medium QC	High QC
Digoxin	Plasma	76	110	95	75	96	78
	Urine	85	92	89	80	97	85
Sotalol	Plasma	81	114	88	77	98	85
	Urine	88	83	94	81	83	101

Table S4. The results of HPLC-MS/MS MRM methods validation.

Analyte	Digoxin			Sotalol		
Matrix	Plasma	Amniotic fluid	Urine	Plasma	Amniotic fluid	Urine
Calibration curve, equation	$y=0.39034*x-0.989$	$y=0.18864*x+0.01461$	$y=0.01519*x+0.00919$	$y=0.29340*x+0.02059$	$y=0.19969*x+0.00537$	$y=0.01417*x-0.00754$
Calibration curve, r	0.99605	0.99868	0.99537	0.99419	0.99397	0.99325
LLOD, ng/ml (digoxin) and µg/ml (sotalol)	0.2	0.2	7.5	0.2	0.2	7.7
LLOQ, ng/ml (digoxin) and µg/ml (sotalol)	0.2	0.5	7.5	0.2	0.2	10.0
Selectivity (STD of the peak area, %)	14.5	10.5	10.5	12.5	9.6	9.6
Matrix effect	93.7±13.9	95.0±4.9	95.0±4.9	91.3±10.1	98.0±11.4	98.0±11.4

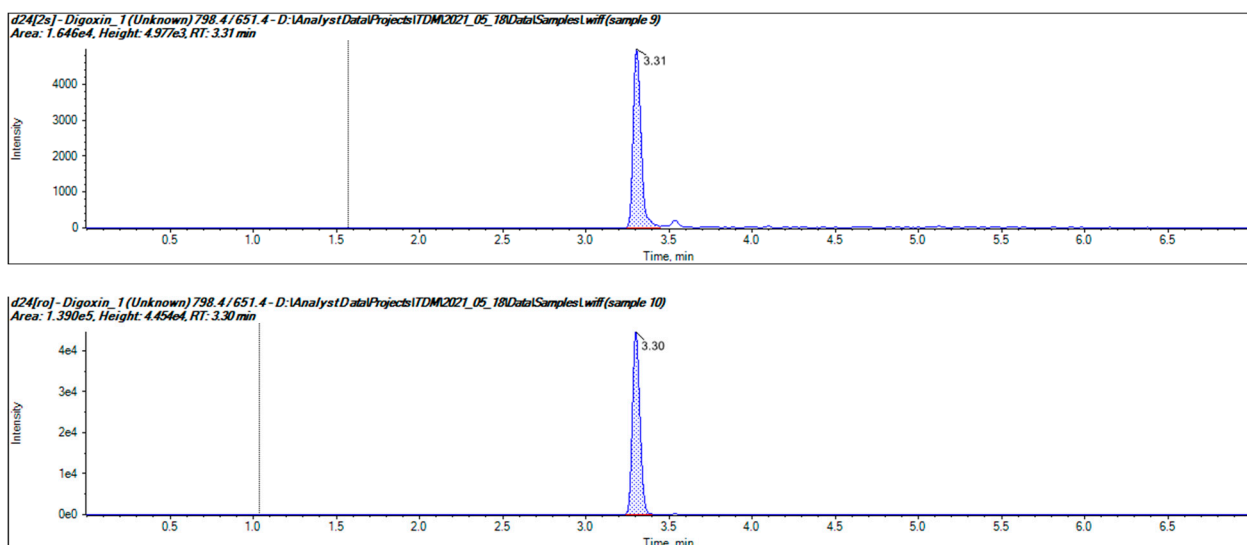
(ME±STD), %						
Recovery (ME±STD), %	82±7.2	89.7±5.2	89.7±5.2	86.7±8.7	88.7±8.7	88.7±8.7
Accuracy, %	(-11.5; -3.2)	(-6.8; -4)	(-3.1; 4.5)	(-0.7; 11.5)	(-0.1; 7.9)	(-7.1, 7)
Precision, %	(3.1; 9.6)	(7.9; 9.2)	(7.9; 12.6)	(8.9; 12.1)	(4.8; 11.9)	(6.7; 12.3)
Robustness (STD of the peak area, %)	4.0	1.5	1.5	3.5	2.0	2.0

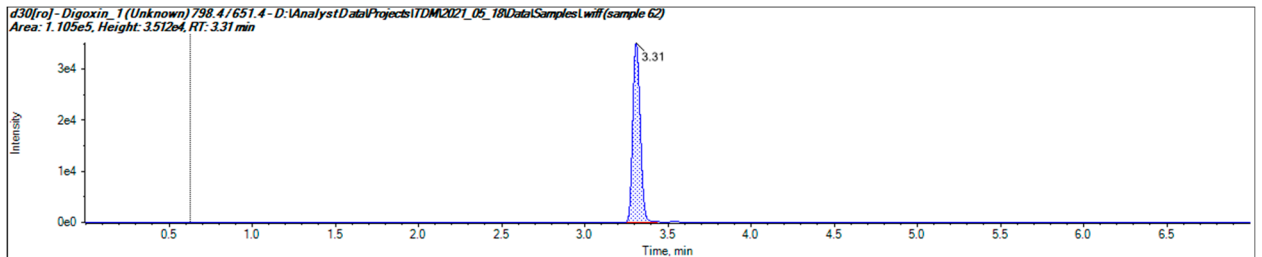
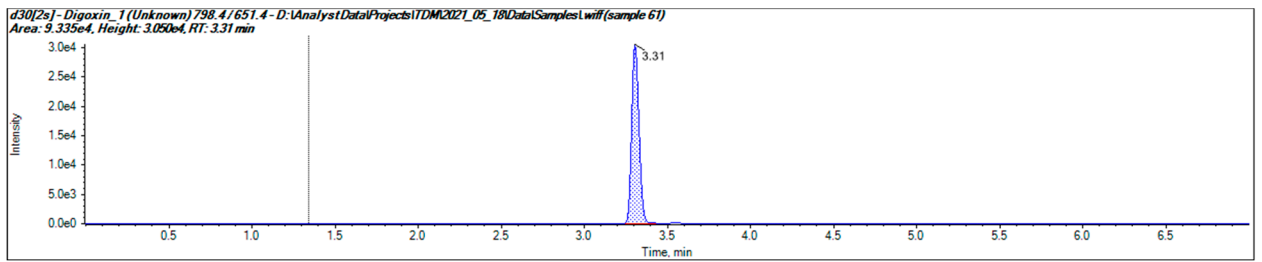
FigureS1: Calibration curve for digoxin in amniotic fluid. Healthy women urine was used as a matrix.



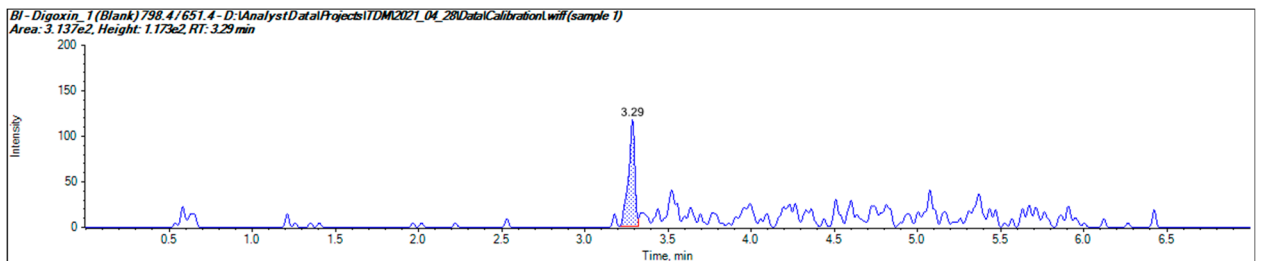
FigureS2: Chromatograms for blank and samples in amniotic fluid for digoxin. The healthy women urine was used as a blank.

1 – Samples:



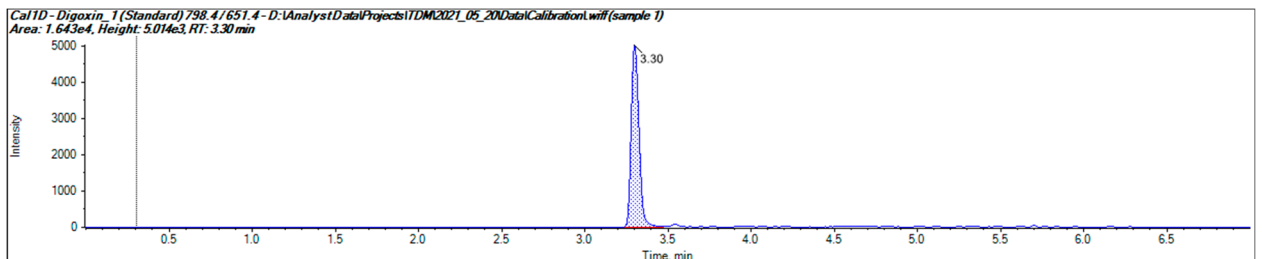


2 – Blank:

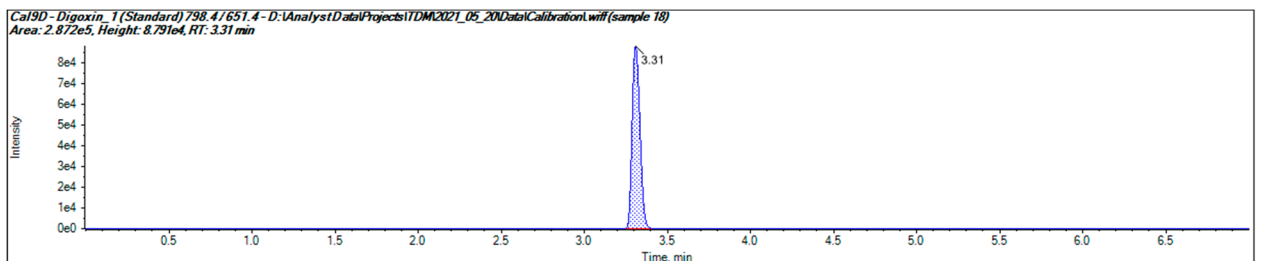


3 – Calibration levels and QC:

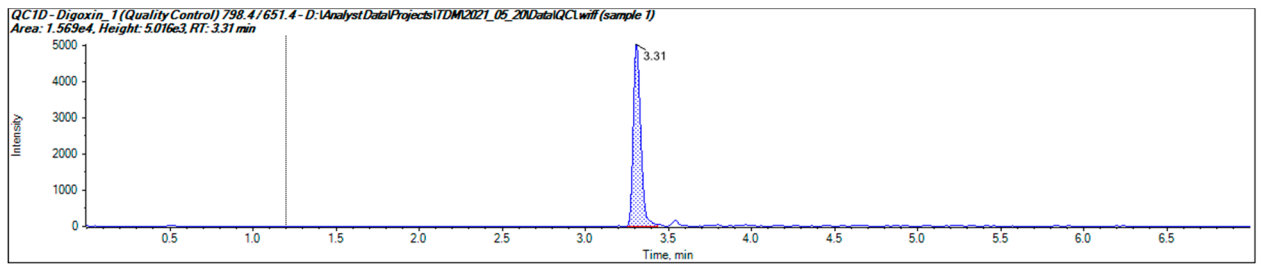
Cal₁Digoxin=0.5 ng/ml



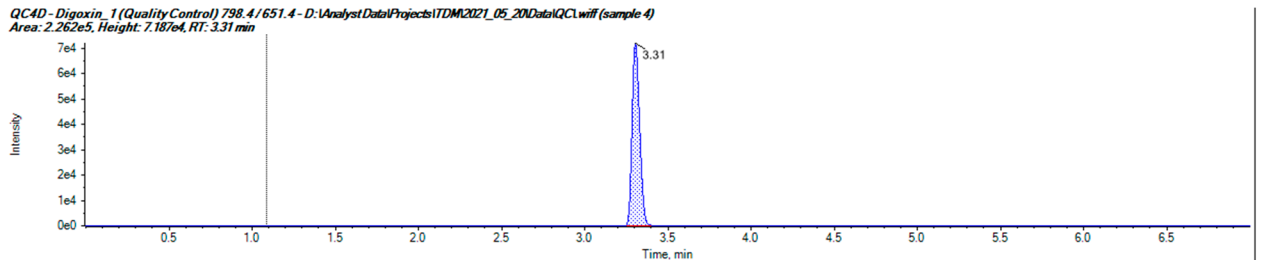
Cal₇Digoxin=10 ng/ml



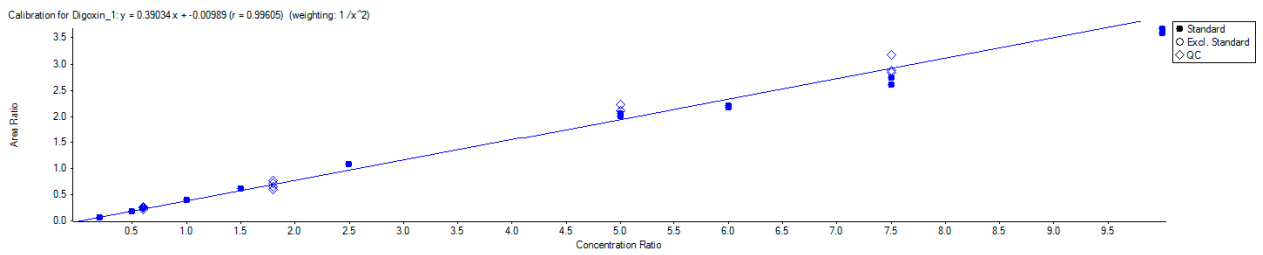
QC₁Digoxin=0.6 ng/ml



QC4Digoxin=7.5 ng/ml

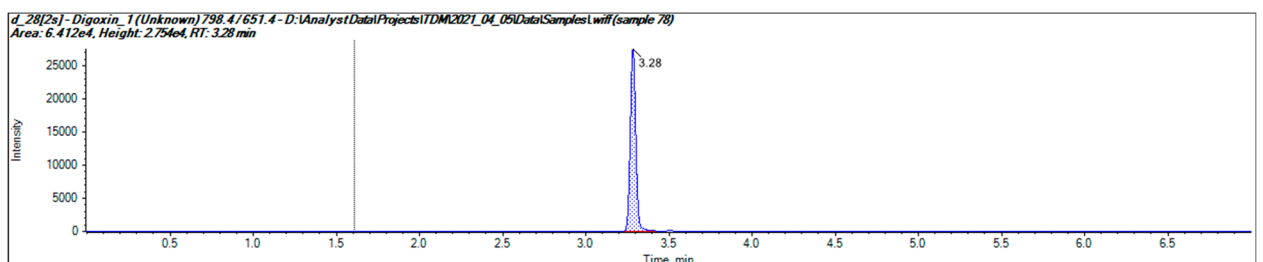
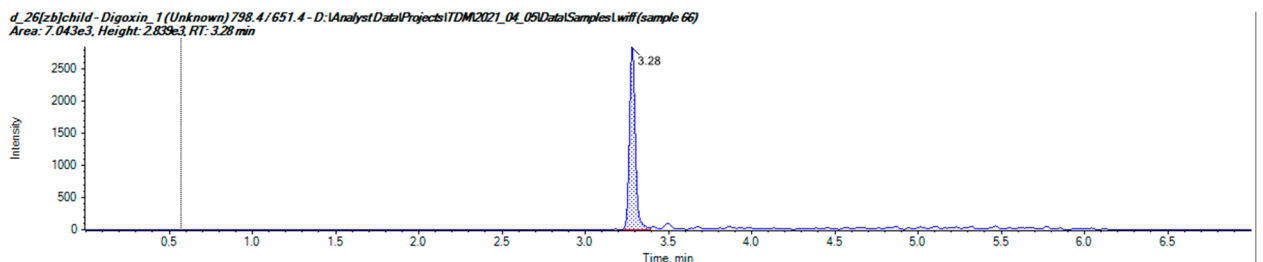


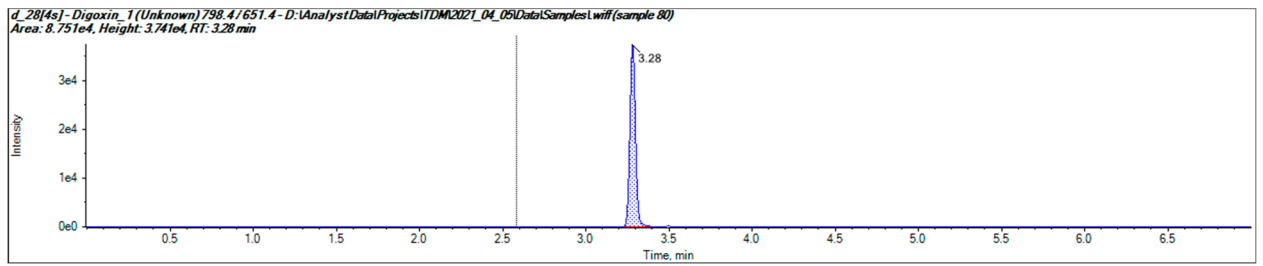
FigureS3: Calibration curve for digoxin in blood. The healthy women plasma was used as a matrix.



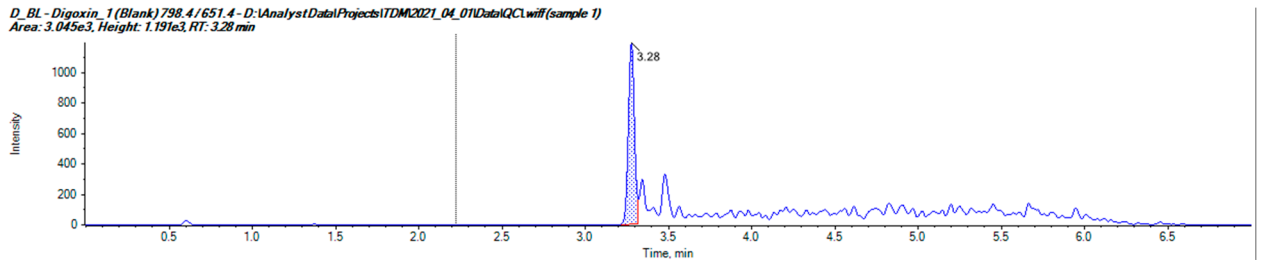
FigureS4: Chromatograms of blank and samples for digoxin on blood.

1 – Samples:



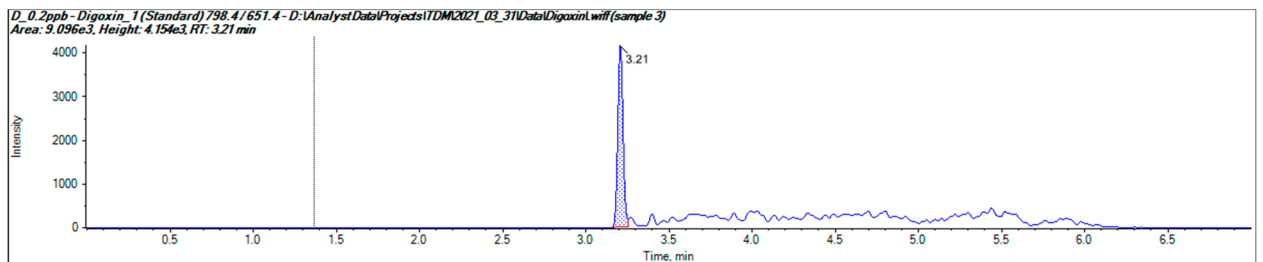


2 – Blank:

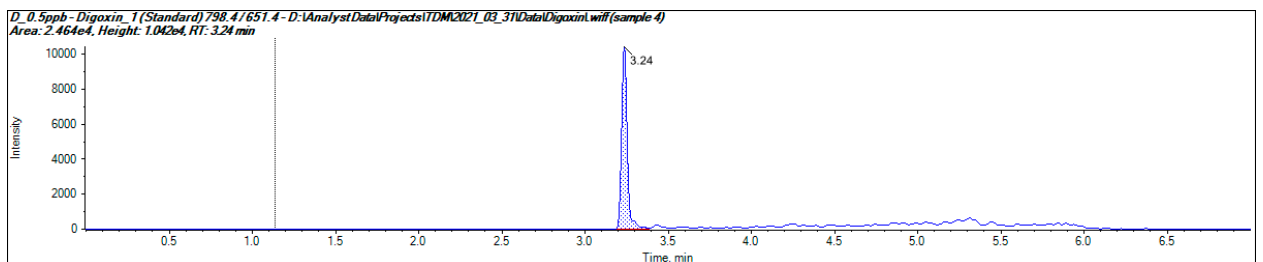


3 – Calibration levels and QC:

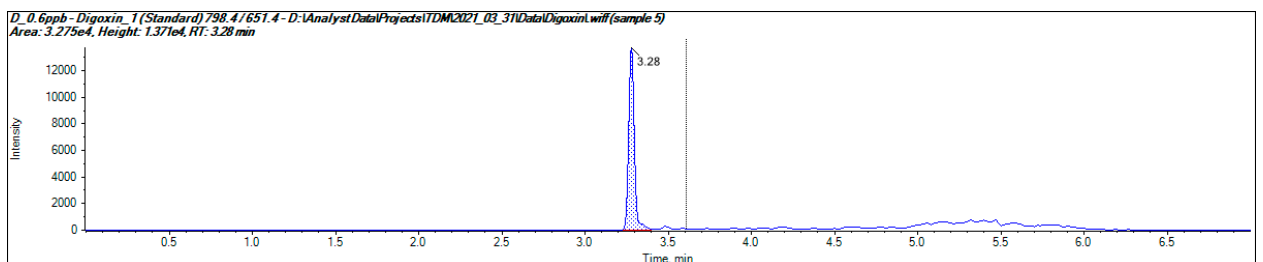
Cal₁Digoxin=0.2 ng/ml



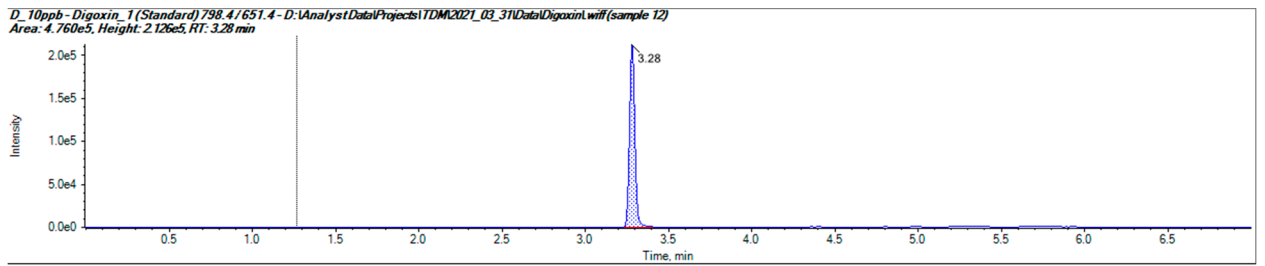
Cal₂Digoxin=0.5 ng/ml



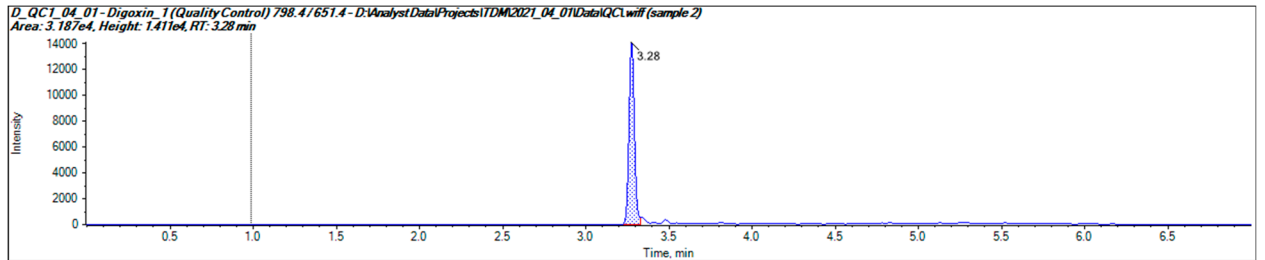
Cal₃Digoxin=0.6 ng/ml



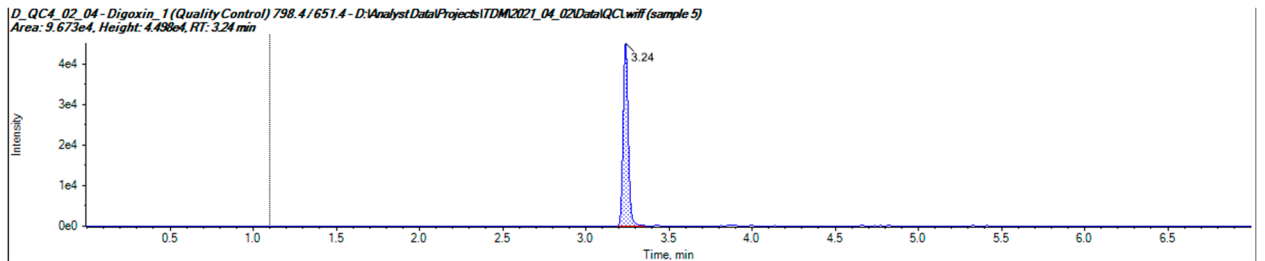
Cal₁Digoxin=10 ng/ml



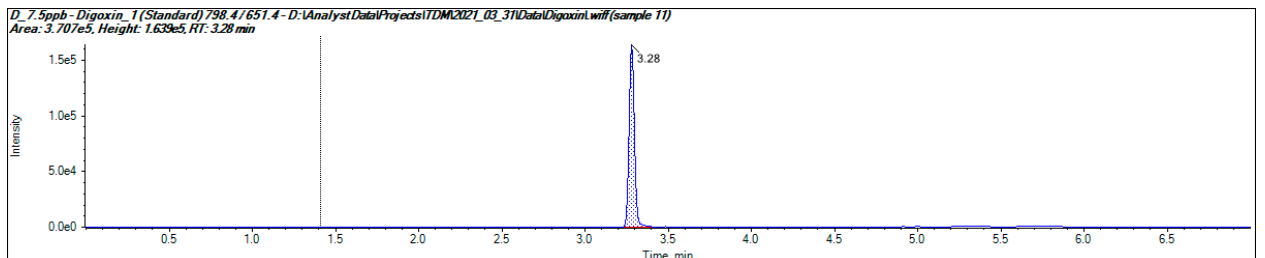
QC₁Digoxin=0.6 ng/ml



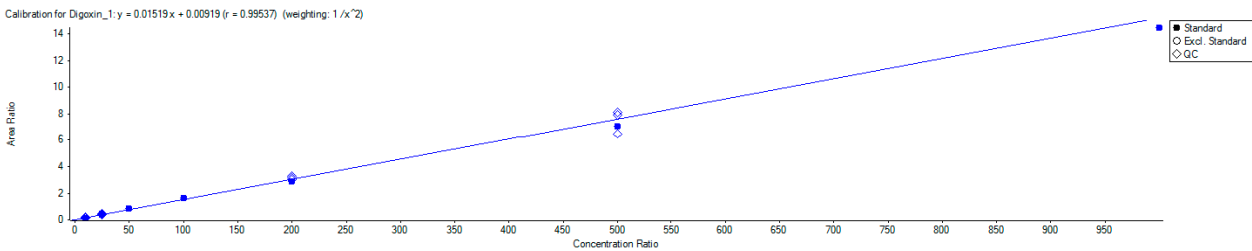
QC₂Digoxin=1.8 ng/ml



QC₄Digoxin=7.5 ng/ml

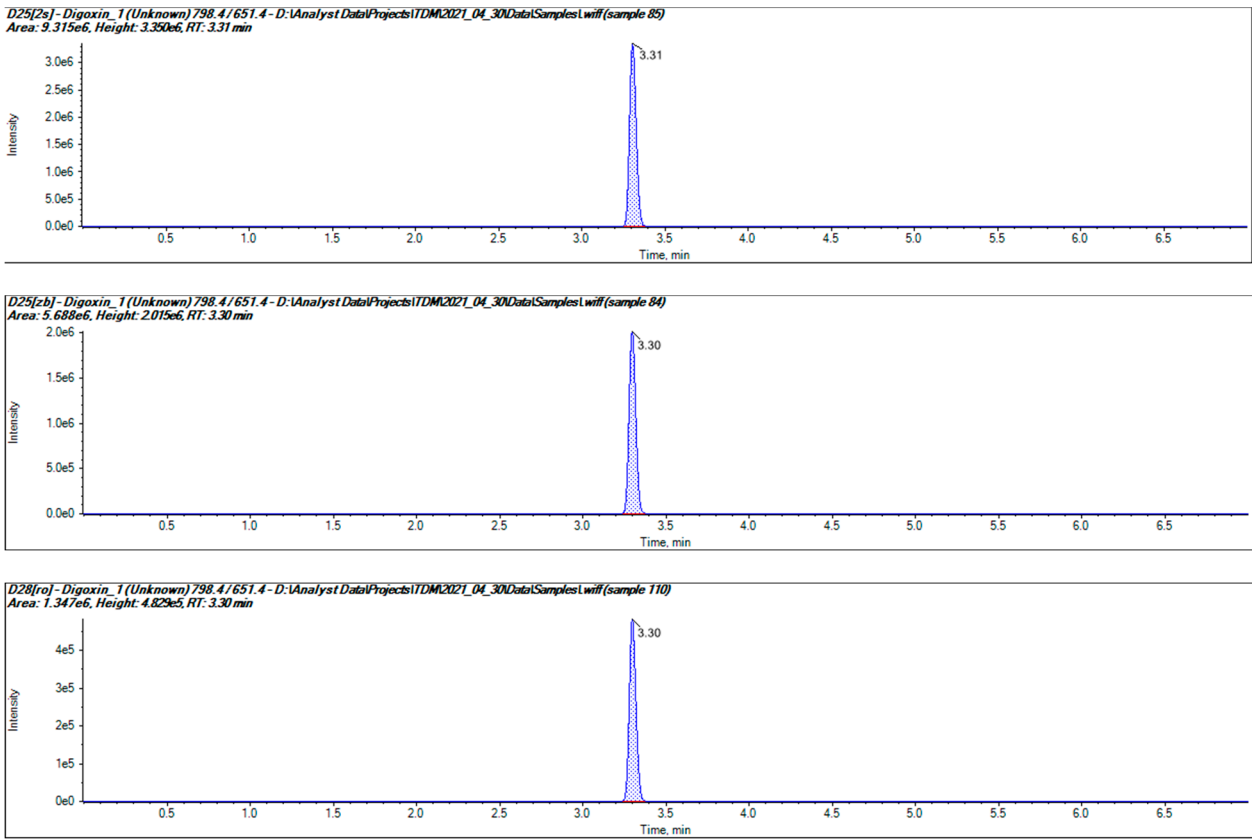


FigureS5: Calibration curve for digoxin in urine. The healthy women urine was used as a matrix.

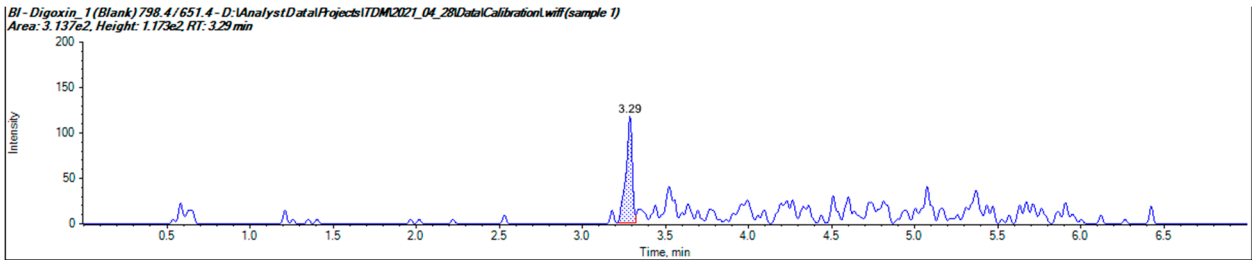


FigureS6: Chromatograms for blank and samples. The healthy women urine was used as a blank.

1 – Samples:



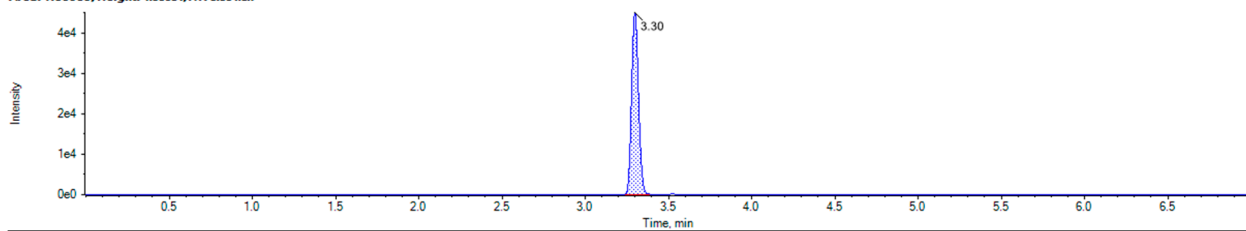
2 – Blank:



3 – Calibration levels:

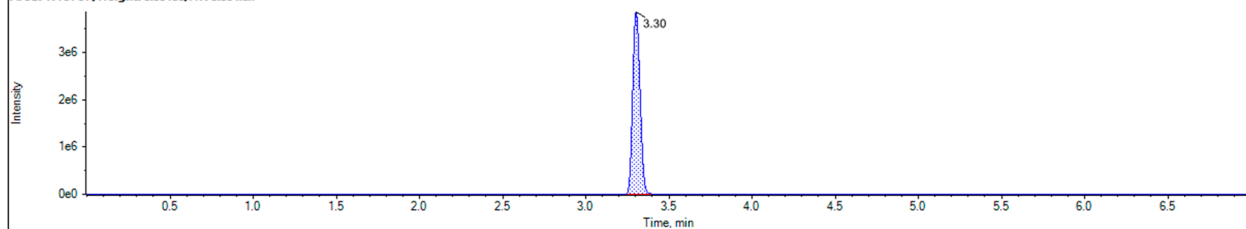
Cal1D-Digoxin_1 (Standard) 798.4/651.4 - D:\AnalystData\Projects\TDM\2021_05_06\Data\Calibration\wiff (sample 2)

Area: 1.309e5, Height: 4.506e4, RT: 3.30 min

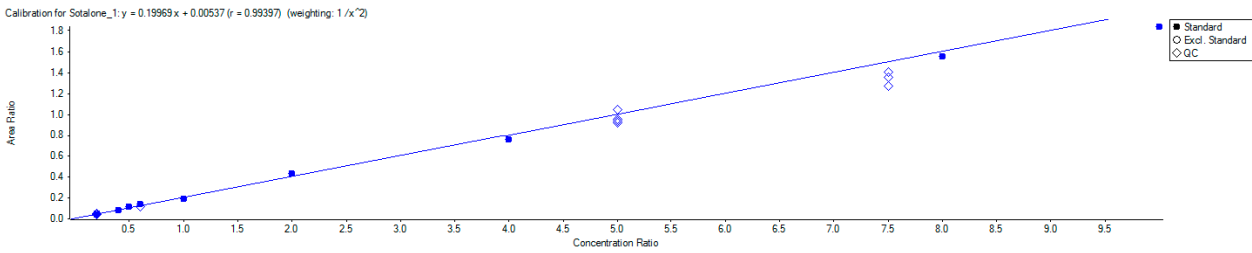


Cal1D-Digoxin_1 (Standard) 798.4/651.4 - D:\AnalystData\Projects\TDM\2021_05_06\Data\Calibration\wiff (sample 9)

Area: 1.187e7, Height: 3.854e6, RT: 3.30 min

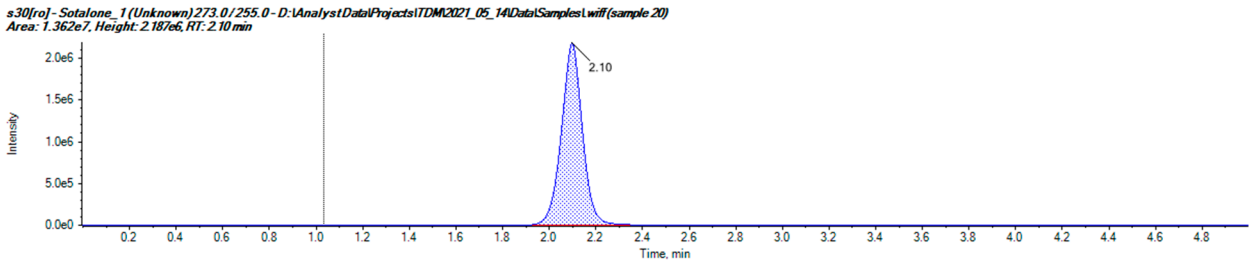
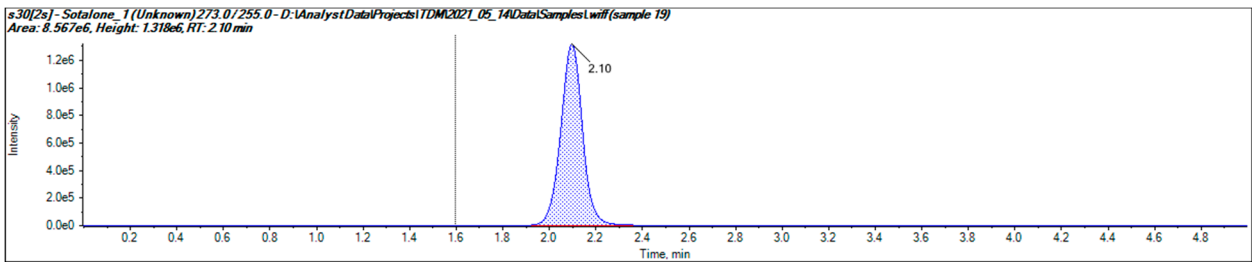
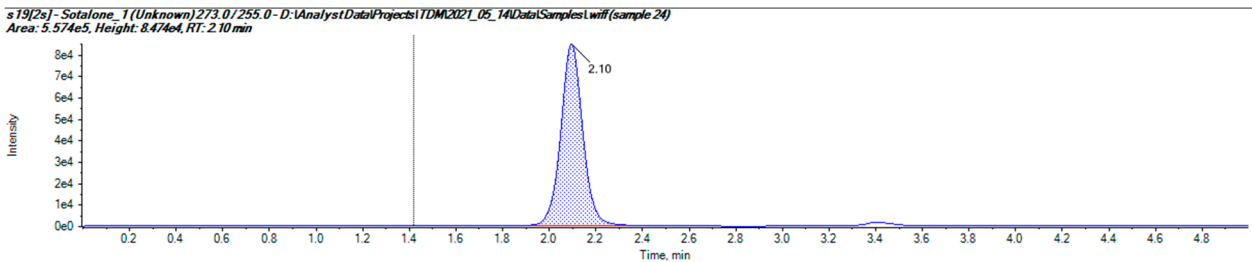


FigureS7: Calibration curve for sotalol in amniotic fluid. The healthy women urine was used as a matrix.

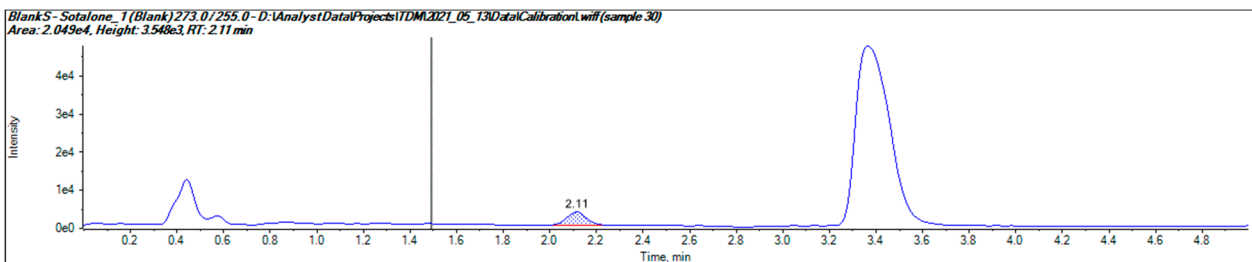


FigureS8: Chromatograms for blank and samples in amniotic fluid for sotalol. The healthy women urine was used as a blank.

1 – Samples:

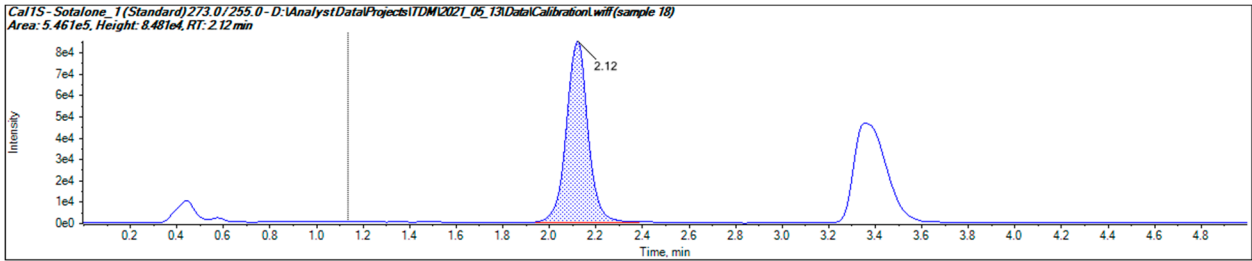


2 – Blank:

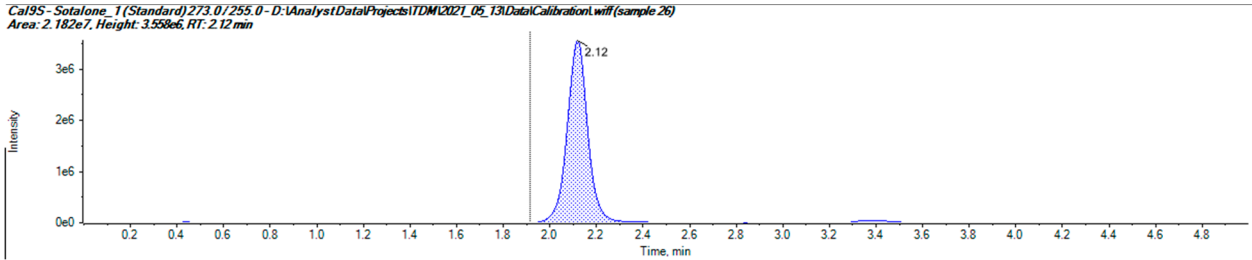


3 – Calibration levels and QC:

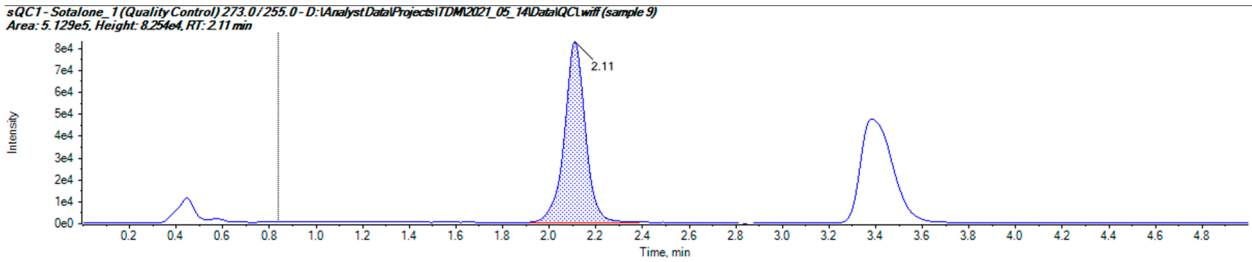
Cal1Sotalol=0.2 µg/ml



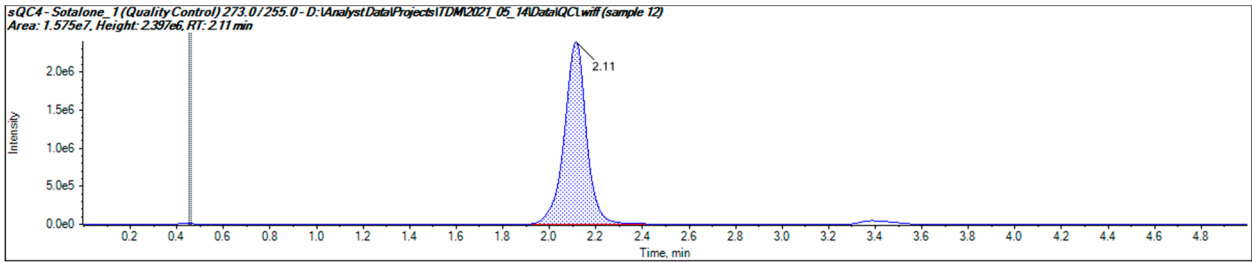
Cal9 Sotalol =10 µg/ml



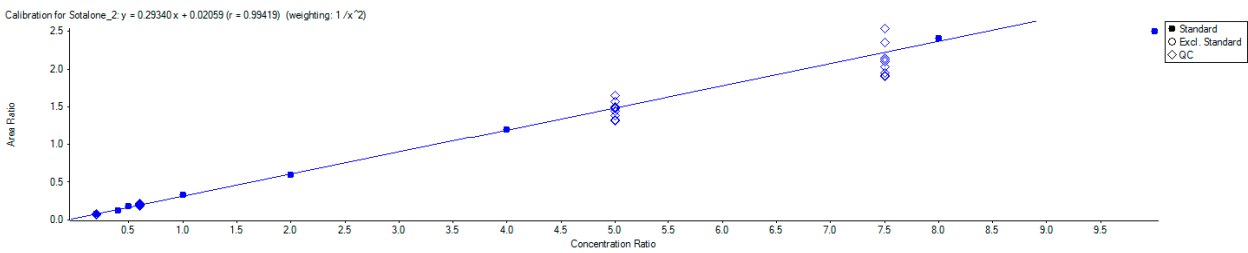
QC1Sotalol=0.2 µg/ml



QC4Sotalol=7.5 µg/ml

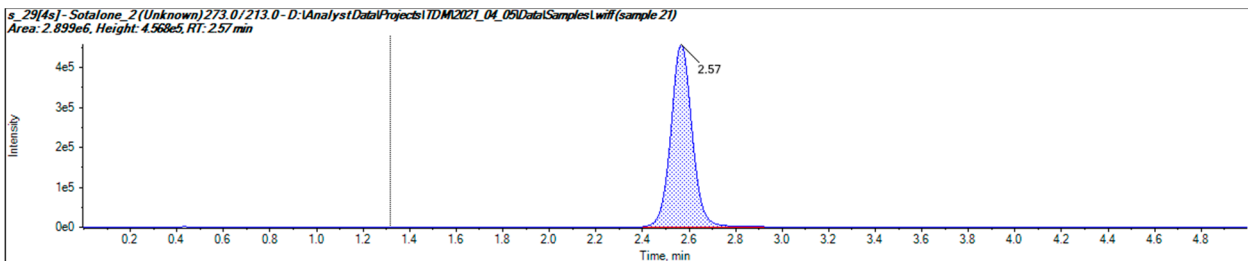
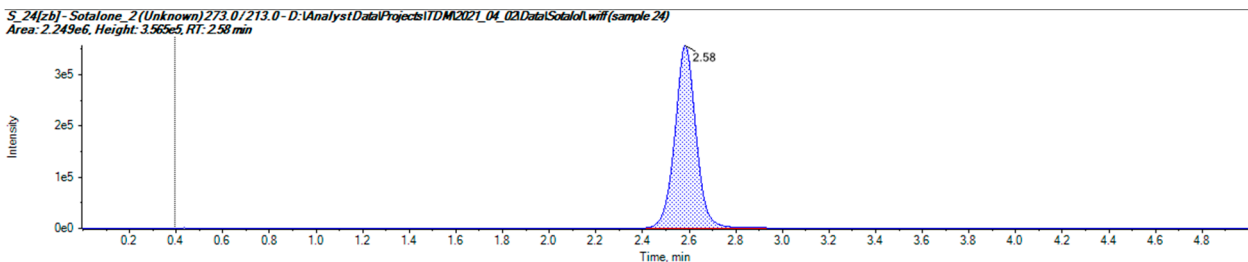
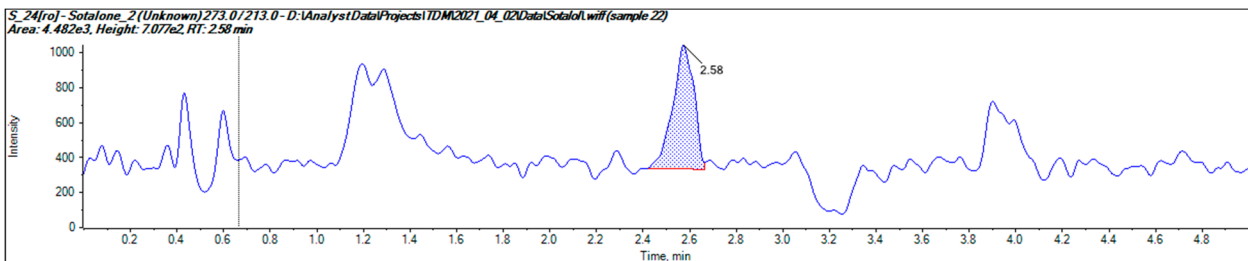
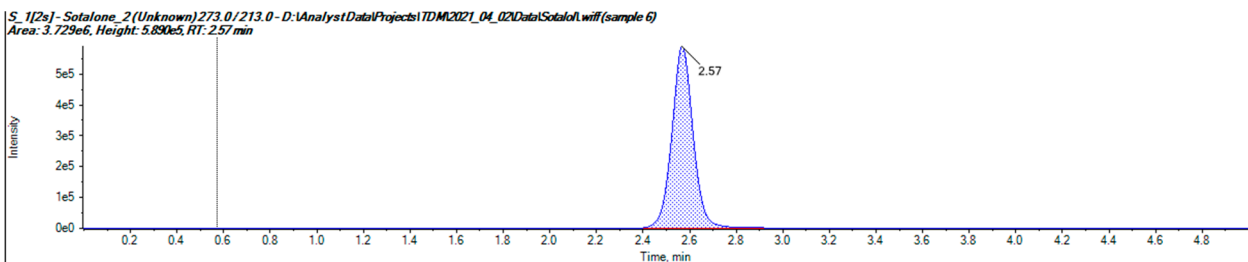


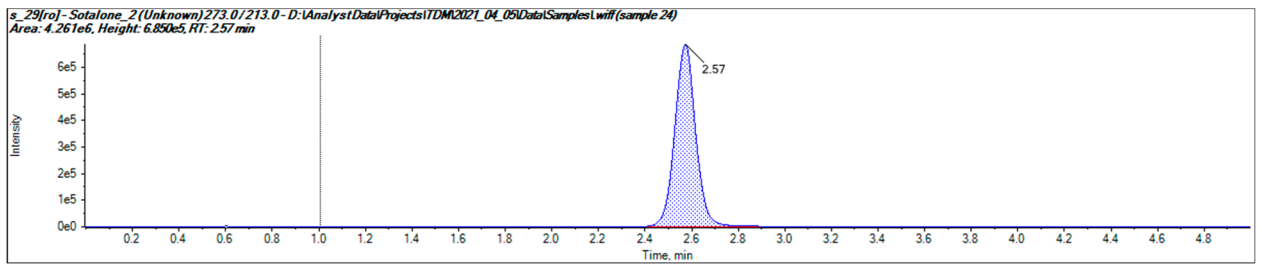
FigureS9: Calibration curve for sotalol in blood. The healthy women plasma was used as a matrix.



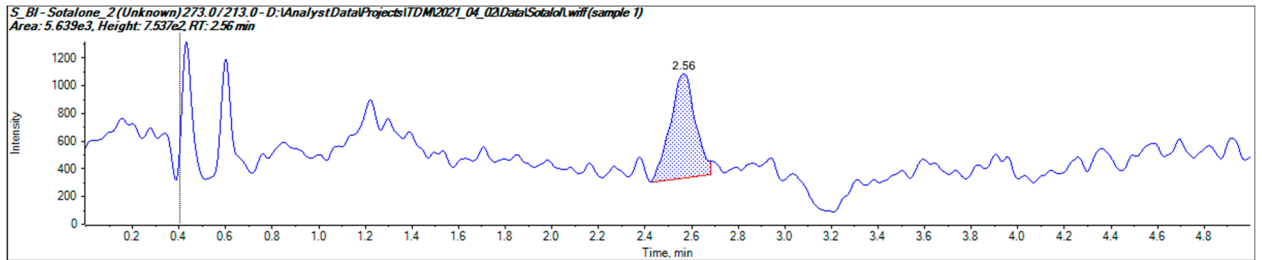
FigureS10: Chromatograms for blank and samples. The healthy women plasma was used as a blank.

1 – Samples:



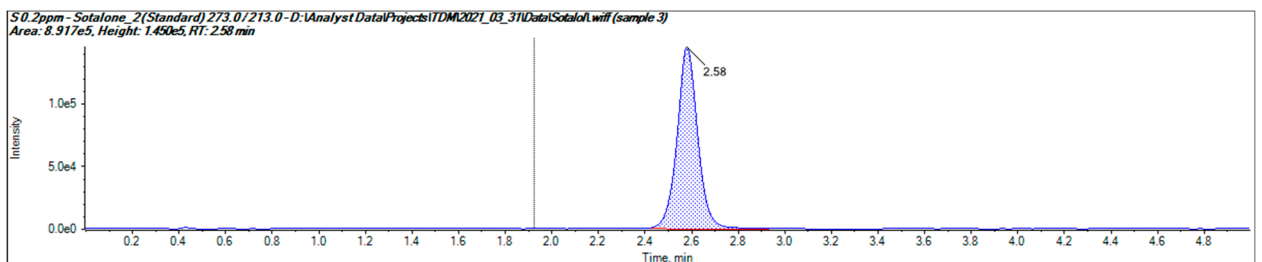


2 – Blank:

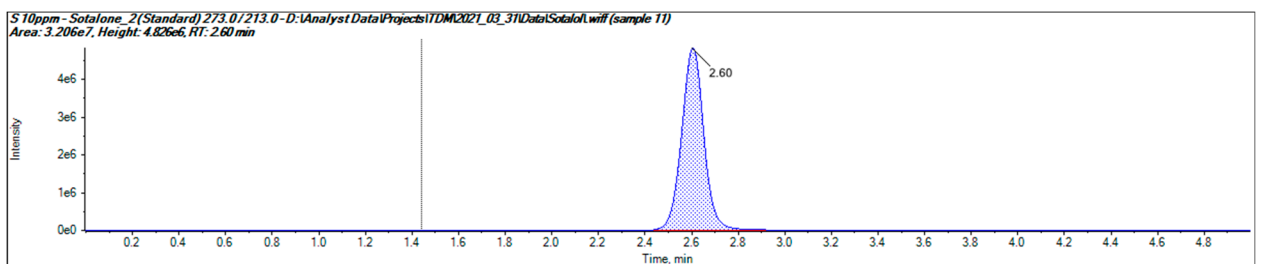


3 – Calibration levels:

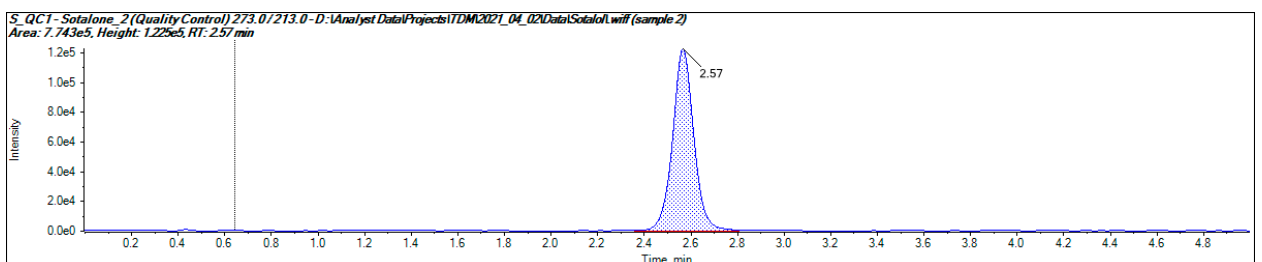
Cal1Sotalol=0.2 µg/ml



Cal9Sotalol=10 µg/ml

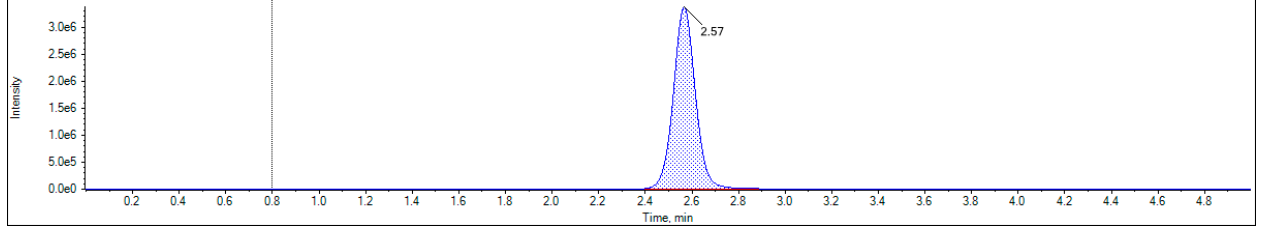


QC1Sotalol=0.2 µg

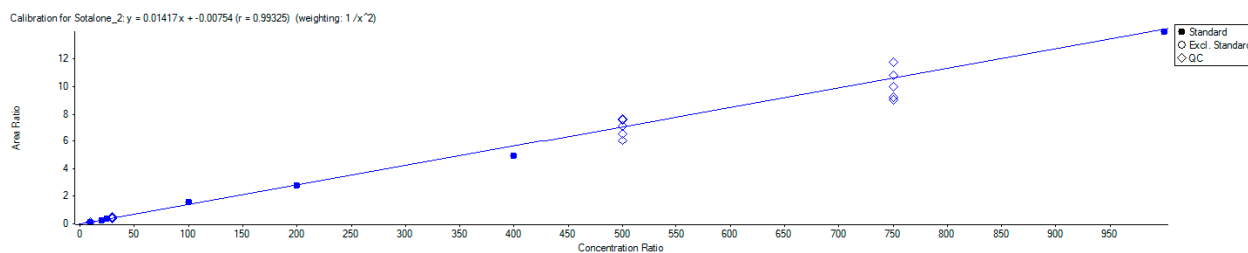


QC4Sotalol=7.5 µg/ml

S_QC4 - Sotalone_2 (Quality Control) 273.0/213.0-D:\Analyst Data\Projects\TDM\2021_04_02\Data\Sotalone.wiff (sample 5)
Area: 2.229e7, Height: 3.37e6, RT: 2.57 min

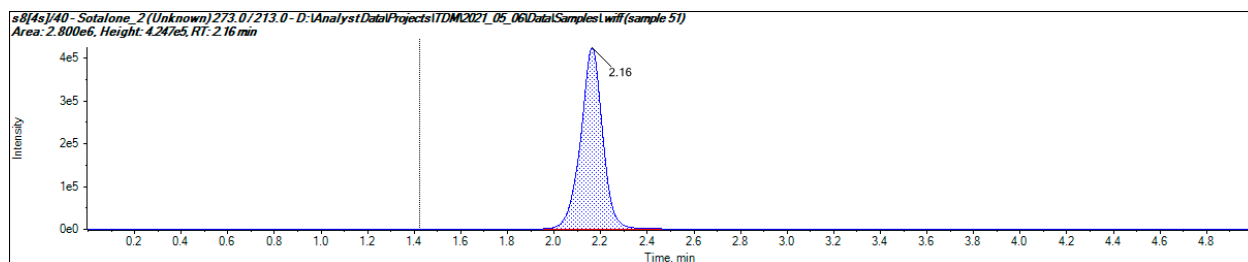
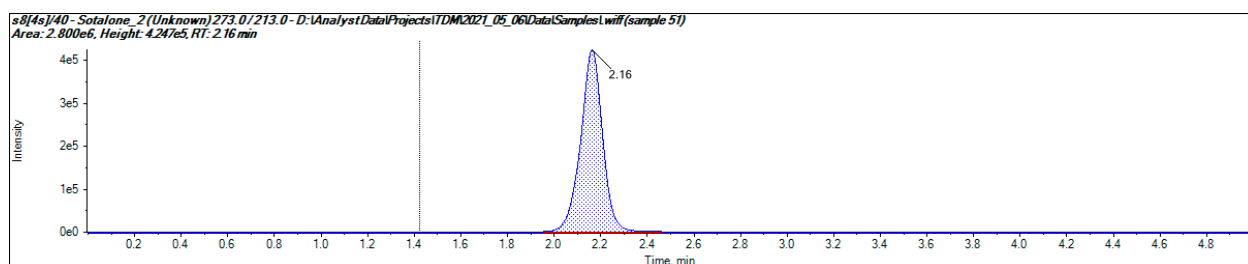
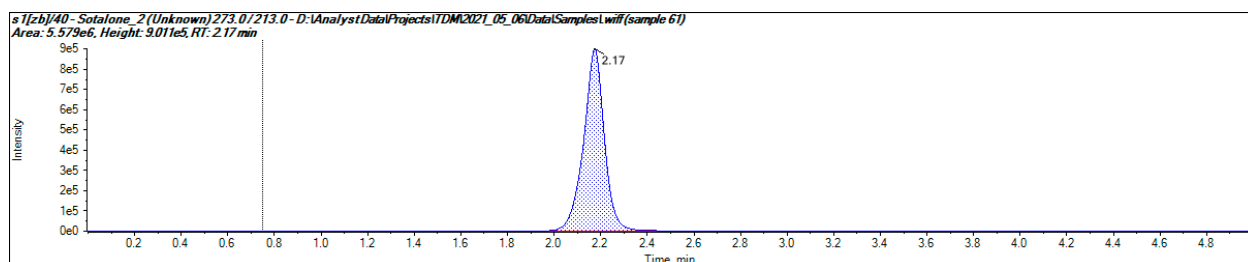


FigureS11: Calibration curve for sotalol in urine. The healthy women urine was used as a matrix.

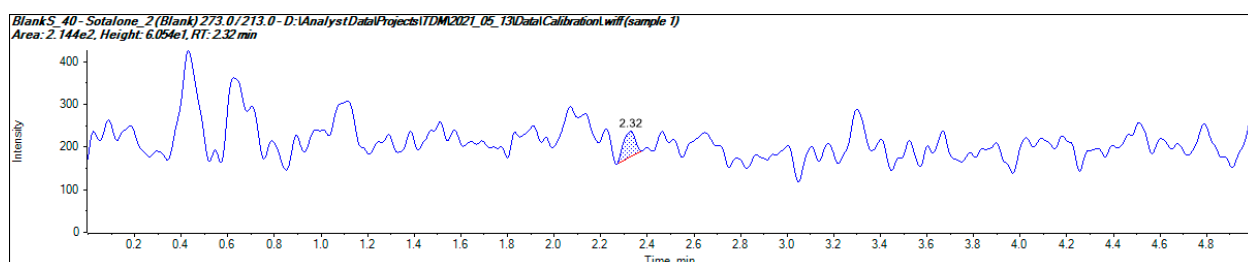


FigureS12: Chromatograms for blank and samples. The healthy women urine was used as a blank.

1 – Samples:

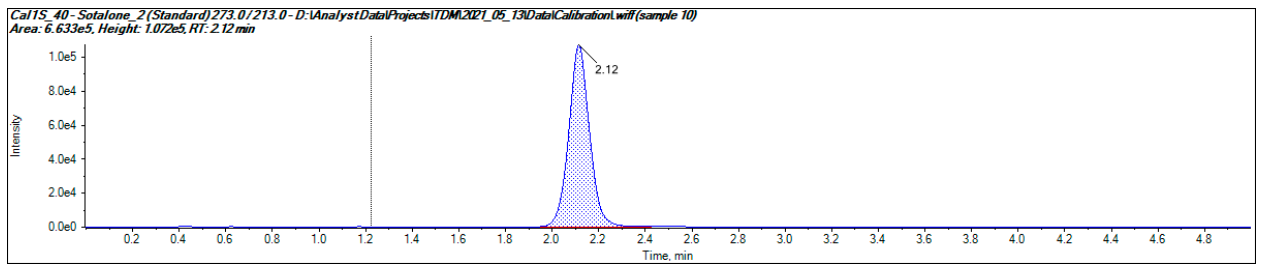


2 – Blank:



3 – Calibration levels:

Cal_{Sotalol} = 10 µg/ml



Cal7Sotalol=1000 $\mu\text{g/ml}$

