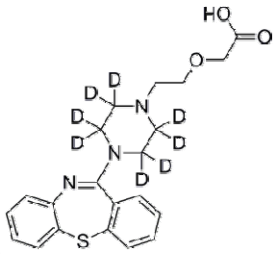
Cerilliant
Analytical Reference Standards
a SIGMA-ALDRICH company

Certified Reference Material - Certificate of Analysis

Cerilliant Quality
ISO GUIDE 34
ISO/IEC 17025
ISO 13485
ISO 15194
ISO 9001
GMP/GLP

Quetiapine Carboxylic Acid-D_8, Primary Measurement Standard

2-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-piperazinyl-D $_8$)ethoxy]-ethanoic acid



Catalog Number: Q-005-1ML
Lot: FN07101704
Retest Date: June 2019
Description: Quetiapine Carboxylic Acid-D_8 in Acetonitrile.
Packaging: Solution in 2 mL amber USP Type I glass ampoule containing not less than 1 mL of certified solution.
Storage: Store unopened in freezer (-10 °C to -25 °C).
Shipping: Ambient. See Stability Section.
Intended Use: This Certified Reference Material is suitable for the *in vitro* identification, calibration, and quantification of the analyte(s) in analytical and R&D applications. Not suitable for human or animal consumption.
Instructions for Use: Users should quantitatively transfer desired volume using established good laboratory practices to spike into matrix or to dilute to the desired concentration. Each ampoule is intended for one-time use.
Safety: **Danger. See Safety Data Sheet**

- Retest Date - stability studies ongoing. Certificate of Analysis will be updated upon completion of retest.
- Ampoules are overfilled to ensure a minimum 1 mL volume can be transferred when using a 1 mL Class A volumetric pipette.
- For quantitative applications, the minimum sample size for intended use is 1 µL.
- For MS Applications, we advise laboratories not to mix lots during a single sequence.

Analyte	Certified Concentration Value
Quetiapine Carboxylic Acid-D_8	100.0 ± 0.5 µg/mL

- Uncertainty of the concentration is expressed as an expanded uncertainty in accordance with ISO 17025 and Guide 34 at the approximate 95% confidence interval using a coverage factor of k = 2 and has been calculated by statistical analysis of our production system and incorporates uncertainty of the mass balance purity factor, material density, balance, and weighing technique.
- This standard is prepared gravimetrically and mass results are reported on the conventional basis for weighing in air. Nominal concentration is calculated based on: the actual measured mass; Mass Balance Purity Factor of the analyte(s); measured mass of the solution; and the density of the pure diluent at 20 °C.
- Concentration is corrected for chromatographic purity, residual water, residual solvents and residual inorganics. No adjustment required before use.
- Additional certification information available upon request.

Metrological Traceability

- This standard has been prepared and certified under the ISO Guide 34, ISO/IEC 17025, ISO 9001 and ISO 13485 standards. This standard meets the requirements of a Certified Reference Material and a Primary Measurement Standard as defined by ISO and is traceable to the SI and higher order standards through an unbroken chain of comparisons.
- This standard has been gravimetrically prepared using balances that have been fully qualified and calibrated to ISO 17025 requirements. All calibrations utilize NIST traceable weights which are calibrated externally by a qualified ISO 17025 accredited calibration laboratory to NIST standards. Qualification of each balance includes the assignment of a minimum weighing by a qualified and ISO 17025 accredited calibration vendor taking into consideration the balance and installed environmental conditions to ensure compliance with USP tolerances of NMT 0.10% relative error. Balance calibration adjustments are performed weekly utilizing the balance's internal adjustment mechanism. Calibration verifications are performed pre-use. Weigh tapes from the calibration verification are included in the production batch record for this standard. Production data package available upon request.
- Fill volume is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- Concentration is verified against an independently prepared calibration solution gravimetrically prepared.
- Each raw material utilized has been identified and thoroughly characterized through the use of multiple analytical techniques. Spectral data is provided on subsequent pages of this COA. The density and material Mass Balance Purity Factor is traceable to the SI and higher order reference standards through mass measurement and instrument qualification and calibrations.

Cerilliant certifies that this standard meets the specifications stated in this certificate and warrants this product to meet the stated acceptance criteria through the expiration/retest date when stored unopened as recommended. Product should be used shortly after opening to avoid concentration changes due to evaporation. Warranty does not apply to ampoules stored after opening.

ANAB ACCREDITED ISO GUIDE 34 REFERENCE MATERIAL PRODUCER

Darron Ellsworth, Quality Assurance Manager

August 07, 2018
Date

Solution Standard Verification

Concentration accuracy and within- and between-bottle homogeneity are analytically verified against an independently prepared calibration solution.

Solution standard verification demonstrates confirmation that the specified requirements for the Primary Measurement Standard have been fulfilled and validated under ISO 13485.

Standard Solution Assay Parameters

Analysis Method:	HPLC/UV
Column:	Ascentis Express C18, 2.7 µm, 3.0 x 100 mm
Mobile Phase:	Acetonitrile:0.1% Ammonium acetate in Water (35:65)
Flow Rate:	1.5 mL/min
Wavelength:	250 nm

Calibration Curve

Calibration Curve:	Linear Regression
Number of Points:	4
Linearity (r) :	1.000

		Verified Concentration (µg/mL)		%RSD - Homogeneity	
Standard Solution	**Lot Number**	**Actual Results**	**Acceptance Criteria**	**Actual Results**	**Acceptance Criteria**
New Lot	FN07101704	101.3	± 3%	0.3	≤ 3%

- Concentration is verified through multiple analyses and is calculated as the average of multiple analyses compared to an independently prepared calibration solution.
- Within-sample and between-sample homogeneity of the New Lot is ensured through rigorous production process controls statistically analyzed to evaluate risk and verified by analysis. Multiple samples pulled from across the lot using a random stratified sampling plan were analyzed to verify homogeneity. % RSD results shown above for the New Lot demonstrate ampoule-to-ampoule homogeneity.

Analyte Certification - Mass Balance Purity Factor

Each analyte is thoroughly identified and characterized using an orthogonal approach. A mass balance purity factor is assigned incorporating chromatographic purity and residual impurities. The mass balance purity factor is utilized to calculate the weighing adjustment necessary to ensure accuracy of the solution standard concentration.

Material Name:	Quetiapine Carboxylic Acid-D_8	**Chemical Formula:**	$C_{21}H_{15}D_8N_3O_3S$
Material Lot:	FN03291701	**CAS Number:**	NA
		Molecular Weight:	405.54

Material Characterization Summary

Analytical Test	**Method**	**Results**	
Primary Chromatographic Purity by HPLC/UV Analysis	SP10-0102	99.2%[1]	
Secondary Chromatographic Purity by LC/MS Analysis	SP10-0107	> 99.9%	
Identity by LC/MS Analysis	SP10-0107	Consistent with Structure	
Isotopic Purity and Distribution by LC/MS SIM Analysis	SP10-0107	0.00% D_0 vs D_8	
		0.00% D_0 to D_5	9.45% D_7
		0.14% D_6	90.41% D_8
Identity by ^{1}H-NMR Analysis	USP <761>, SP10-0116	Consistent with Structure	
Residual Solvent Analysis by GC/FID Headspace	AM1087 [2]	None Detected	
Residual Water Analysis by Karl Fischer Coulometry	AM1346 [2]	0.61%	
Inorganic Content by Microash Analysis	SP10-0135	< 0.2%	
Mass Balance Purity Factor		98.58%	

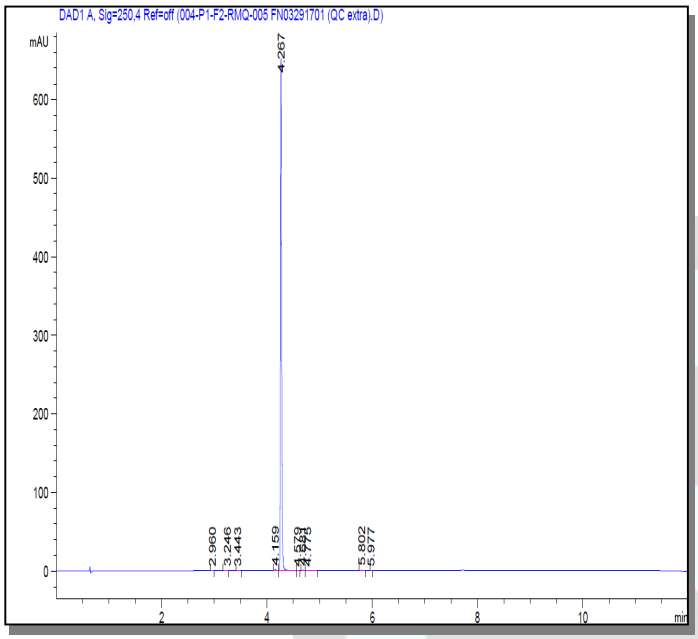
- The primary chromatographic purity is calculated as the average of two independently performed analyses utilizing two different methods. Acceptance criteria requires the purity values to be within 0.5% of each other.
- The primary chromatographic purity value is used to calculate the Mass Balance Purity Factor.
- A secondary chromatographic purity method is utilized as a control.
- Mass Balance Purity Factor = [(100 - wt% residual solvent - wt% residual water - wt% residual inorganics) x Chromatographic Purity/100].
- Mass Balance Purity Factor does not include adjustment for chiral and/or isotopic purity.

[1] 0.01% Quetiapine-D_8 detected by HPLC/UV analysis. No Norquetiapine-D_8 detected.

[2] Validated analytical method

Spectral and Physical Data

HPLC/UV



Column: Ascentis Express C18, 2.7 µm, 3.0 x 100 mm

Mobile Phase: A: Acetonitrile
B: 0.1% Ammonium acetate in Water

Gradient:

Time (min)	% A	% B
0.0	15	85
8.0	70	30
10.0	70	30
10.1	15	85

Flow Rate: 0.7 mL/min

Wavelength: 250 nm

Data File Name: RMQ-005 LC 13 2017-06-20 17-59-24\004-P1-F2.D

Instrument: LC#13

Sample Name: FN03291701

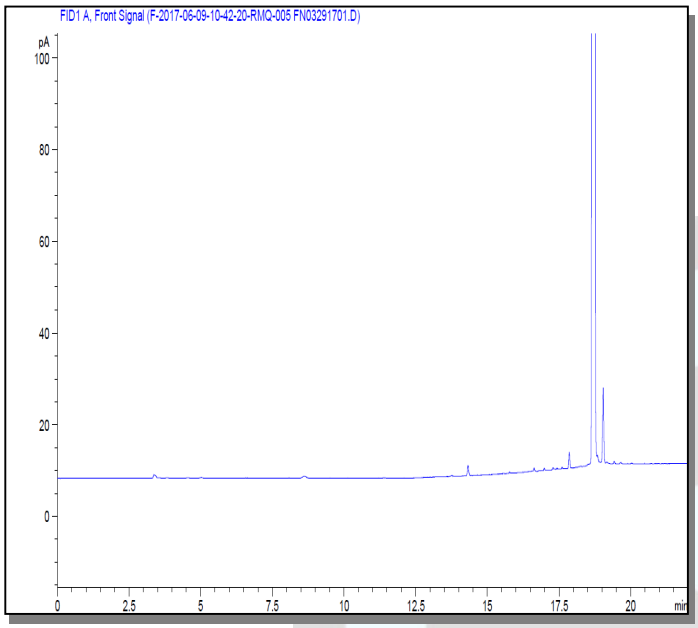
Acquired: June 20, 2017

Peak #	Ret Time	Area	Height	Area %
1	2.96	0.19	0.09	0.02
2	3.25	0.12	0.05	0.01
3	3.44	0.44	0.21	0.04
4	4.16	2.48	1.36	0.25
5	4.27	1002.40	650.89	99.28
6	4.58	0.14	0.05	0.01
7	4.68	1.27	0.84	0.13
8	4.78	1.50	0.29	0.15
9	5.80	1.08	0.60	0.11
10	5.98	0.10	0.05	0.01

Peak 10 has been identified as Quetiapine-D_8

Spectral and Physical Data (cont.)

Residual Solvent Analysis by GC/FID Headspace



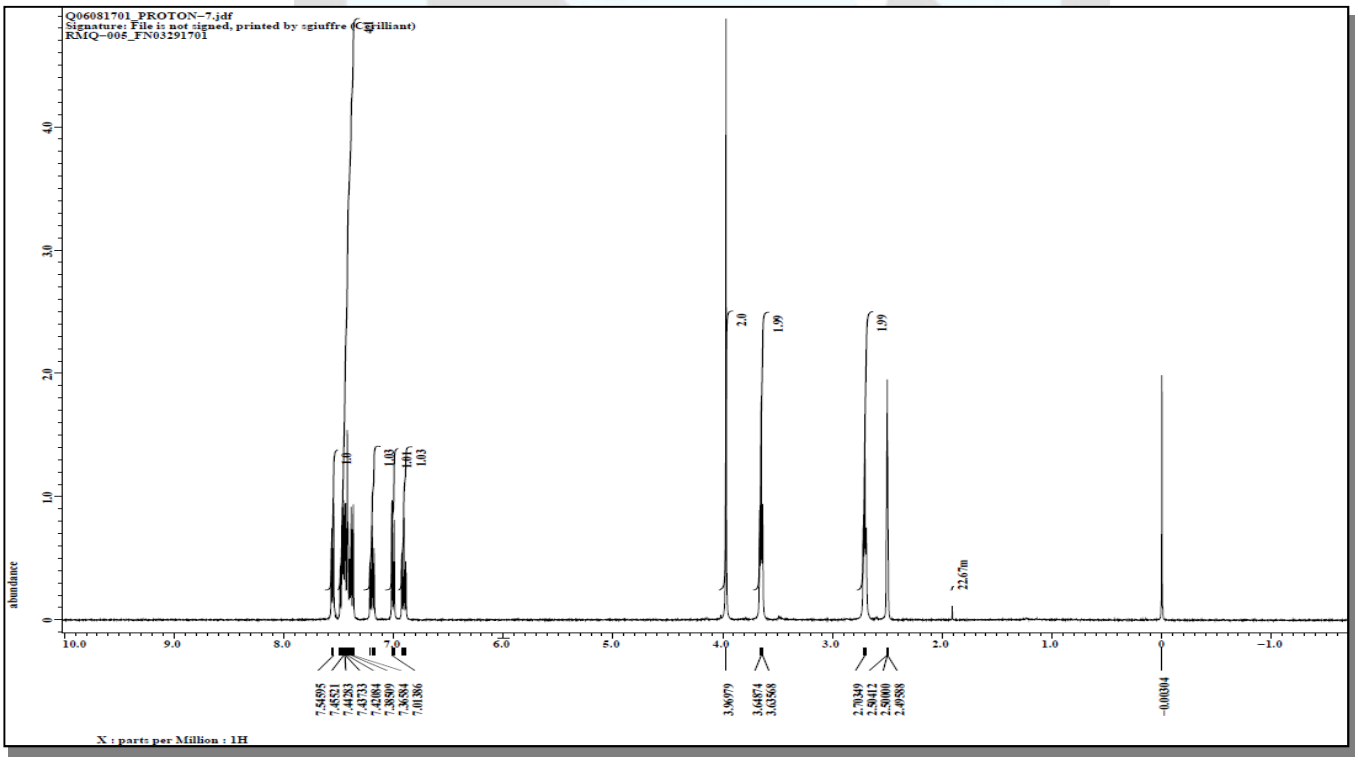
Column:	DB-ALC1 30 m x 0.53 mm, 3 µm film thickness
Temp Program:	40°C (12 min) to 220°C at 40°C/min (5.5 min)
Carrier Gas:	Helium
Flow Rate:	2.0 mL/min
Detector Heater Temp:	250°C
Injector:	Headspace Sampler
HS Oven Temp:	60°C
Vial Equilibration:	10 minutes
Data File Name:	2017-06-09 10-08-41\F-2017-06-09-10-42-20.D
Instrument:	GC#11
Sample Name:	FN03291701
Acquired:	June 09, 2017

Peak	Compound	Area	Weight %
1	NMP	NA	NA
Total			**ND**

ND - None Detected

^{1}H NMR

Instrument: JEOL ECS 400
Solvent: DMSO-D_6



Spectral and Physical Data (cont.)

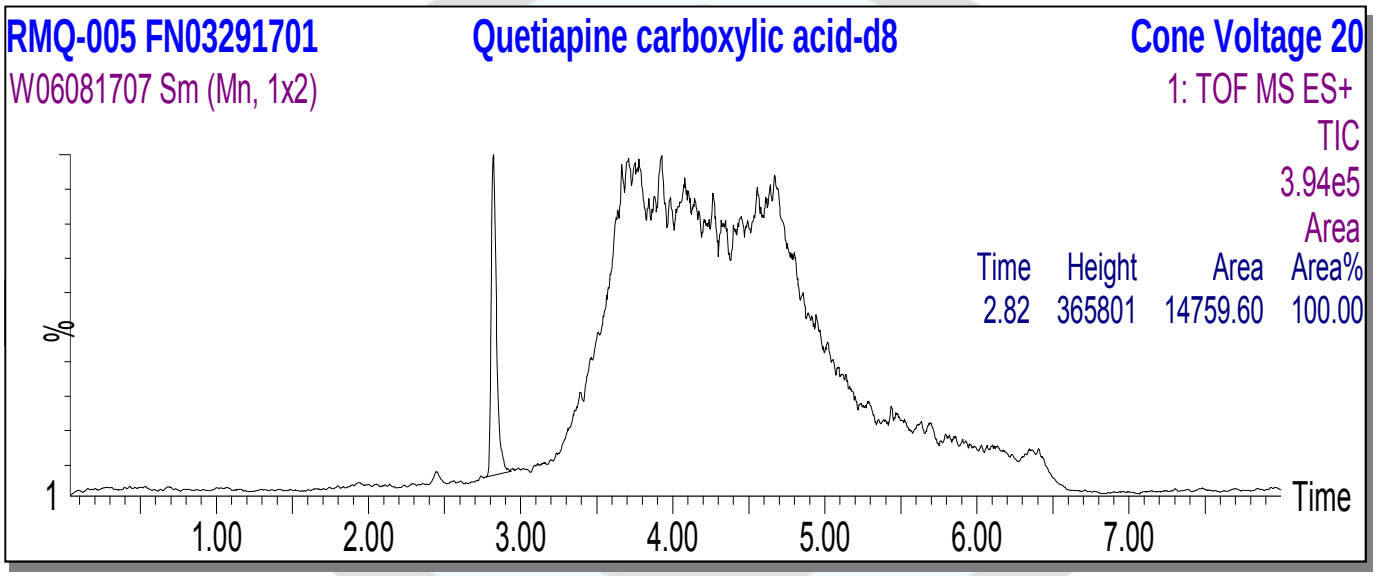
LC/MS

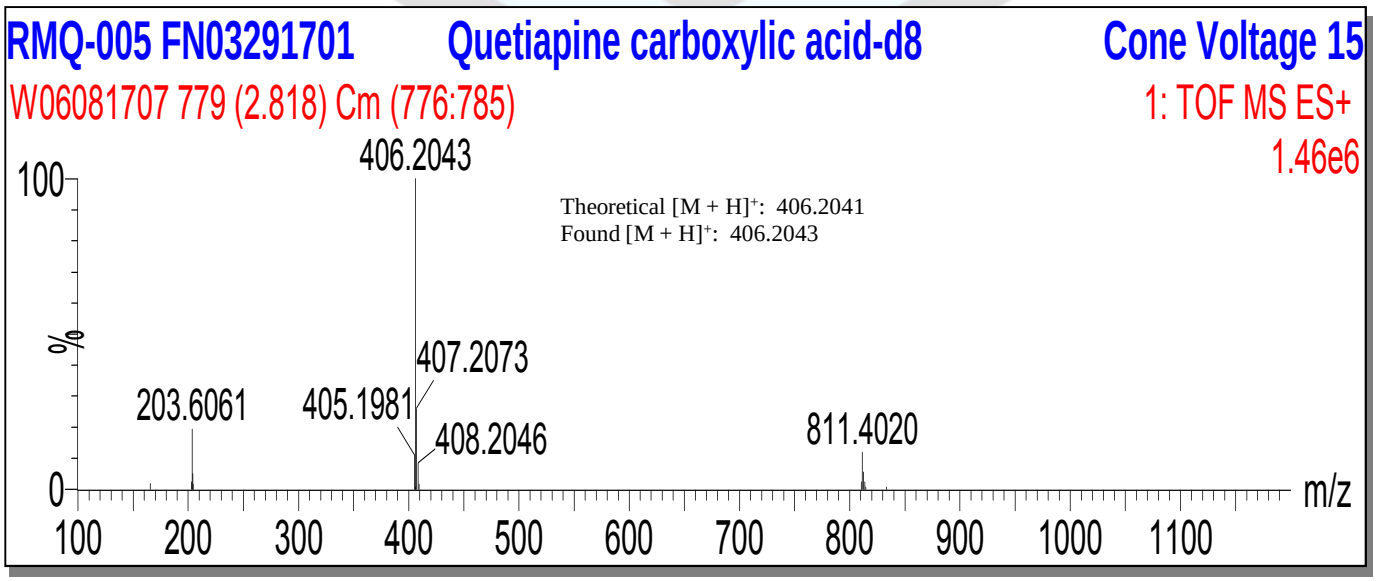
Column:	Ascentis Express C18, 2.7 µm, 3.0 x 50 mm
Mobile Phase:	A: 0.1% Formic acid in Water
	B: Acetonitrile

Gradient:

Time (min)	% A	% B
0.0	90	10
0.5	90	10
4.0	50	50
5.8	50	50
6.0	90	10
8.0	90	10

Flow Rate:	0.4 mL/min
Scan Range:	100 - 1200 amu
Ionization:	Electrospray, Positive Ion
Data File Name:	W06081707
Instrument:	Waters XEVO G2 QTOF
Sample Name:	FN03291701
Acquired:	June 08, 2017





Spectral and Physical Data (cont.)

Isotopic Purity by LC/MS SIM

Column: Ascentis Express C18, 2.7 µm, 3.0 x 50 mm

Mobile Phase: A: 0.1% Formic acid in Water
B: Acetonitrile

Gradient:

Time (min)	% A	% B
0.0	90	10
0.5	90	10
4.0	50	50
5.8	50	50
6.0	90	10
8.0	90	10

Flow Rate: 0.4 mL/min

Scan Range: 398 - 406 amu

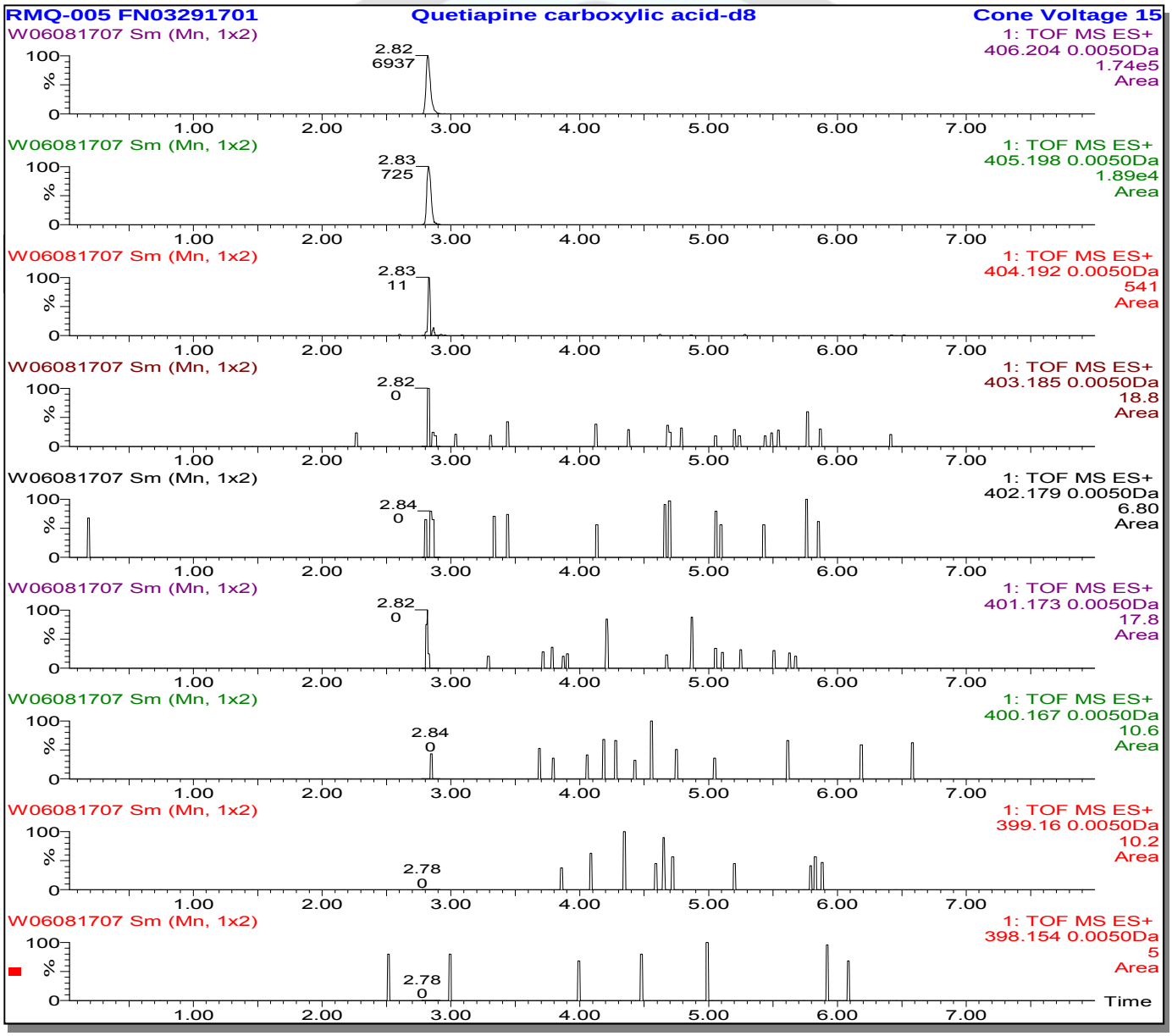
Ionization: Electrospray, Positive Ion

Data File Name: W06081707

Instrument: Waters XEVO G2 QTOF

Sample Name: FN03291701

Acquired: June 08, 2017



Stability

Short term stability studies have been performed under accelerated conditions for a period of up to one week. Short term data is utilized to predict long term stability and to support transport conditions and normal laboratory use. Real-time stability studies are performed at the recommended storage conditions over the life of the product.

Short Term Stability: *A summary of accelerated stability findings for a related product (Q-004-1ML, Quetiapine carboxylic acid) is listed below.*

Storage Condition	Mean Kinetic Temperature (MKT)	Time Period/Result
Freezer	-15°C	No decrease in purity was noted after one week.
Refrigerator	4°C	
Room Temperature	21°C	
40°C	40°C	

Transport/Shipping: *Stability studies support the transport of this product at ambient conditions.*

Long Term Stability: *Long term stability has been assessed for Freezer storage (-10 °C to -25 °C) conditions. Stability of a minimum of 11 months has been established through real-time stability studies.*

COA Revision History

Revision No.	Date	Reason for Revision
00	July 25, 2017	Initial version
01	August 07, 2018	Revised Retest Date from September 2018 to June 2019
		Added Long Term Stability section.