

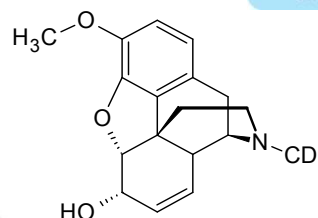
Certificate of Analysis

Codeine-D₃

7,8-Didehydro-4,5-epoxy-3-methoxy-17-trideuteromethylmorphinan-6-ol

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

Catalog Number: C-007
Solution Lot: FE081012-03
Expiration Date: August 2017
Solvent: Methanol
Volume per Ampule: Not less than 1 mL
Storage: Store unopened in freezer.
Shipping: Ambient. See Stability Section.
Intended Use: For R&D/ analytical purposes only. Not suitable for human or animal consumption.
Regulatory: USDEA Exempt | Canadian TK# 61-18



Safety: Danger. See Safety Data Sheet

- Expiration Date has been established through real time stability studies.
- Ampules are overfilled to ensure a minimum 1 mL volume fill. We advise laboratories to use measured volumes of this standard solution before diluting to the desired concentration.
- 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.

Component	Solution Purity	Certified Concentration
Codeine-D ₃	99.3%	1.000 ± 0.006 mg/mL
<ul style="list-style-type: none"> 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 purity factor, material density, and balance and weighing technique. This standard is prepared gravimetrically and mass results are reported on the conventional basis for weighing in air. Concentration is calculated based on: the actual measured mass; 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. 		

Solution Standard Verification and Homogeneity


Standard Solution	Lot Number	Verified Concentration (mg/mL)		%RSD - Homogeneity	
		Actual Results	Acceptance Criteria	Actual Results	Acceptance Criteria
New Lot	FE081012-03	0.981	± 3%	0.7	≤ 3%
Previous Lot	FE050311-04	1.004	± 3%		
<ul style="list-style-type: none"> Concentration is verified through multiple analyses and is calculated as the average of multiple analyses compared to an independently prepared calibration solution. Homogeneity of the New Lot is ensured through rigorous production process controls statistically analyzed to evaluate risk and verified by analysis. The % RSD of samples pulled from across the lot demonstrate homogeneity of the New Lot. 					

Traceability

- Gravimetrically prepared using qualified balances calibrated semi-annually by Mettler Toledo using NIST traceable weights. Calibration verification performed weekly and prior to each use utilizing NIST traceable weights. Each balance has been assigned a minimum weighing by Mettler Toledo taking into consideration the balance and installed environmental conditions to ensure weighing complies with USP tolerances of no more than 0.1% relative error.
- Concentration is verified against an independently prepared calibration solution gravimetrically prepared using balances calibrated to NIST.
- In addition, each neat material utilized has been identified and thoroughly characterized through the use of multiple analytical techniques. Spectral data is provided on subsequent pages of the COA.

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.




 Darron Ellsworth, Quality Assurance Manager

April 28, 2015

Date

Standard Solution Assay Parameters

Analysis Method: UV/Vis
Wavelength: 285 nm
Slit Width: 1.0 nm
Response: 0.5 s

Calibration Curve

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

Neat Material Data

Compound Name: Codeine-D₃
Compound Lot: FC102110-01

Chemical Formula: C₁₈H₁₈D₃NO₃
CAS Number: 70420-71-2
Molecular Weight: 302.35

Neat Material Characterization Summary

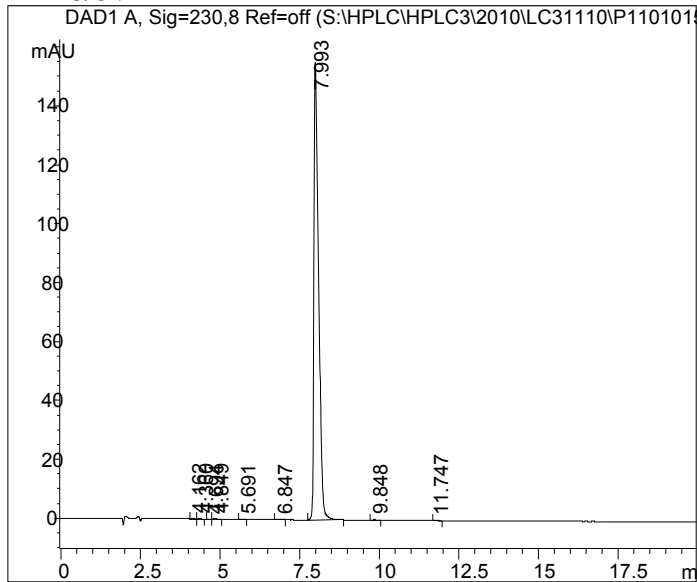
Analytical Test	Method	Results
Primary Chromatographic Purity by HPLC/UV Analysis	SP10-0102	99.6%
Secondary Chromatographic Purity by GC/FID Analysis	SP10-0101	99.6%
Identity by LC/MS Analysis	SP10-0107	Consistent with Structure
Isotopic Purity and Distribution by LC/MS SIM Analysis	SP10-0107	0.00% D ₀ vs D ₃
		0.00% D ₀ 1.72% D ₂
		0.03% D ₁ 98.26% D ₃
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	USP <921>, SP10-0103	0.01%
Inorganic Content by Microash Analysis	SP10-0135	< 0.2%
Purity Factor		99.57%

- Primary 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 Purity Factor.
- A secondary chromatographic purity method is utilized as a control.
- Purity Factor = [(100 - wt% residual solvent - wt% residual water - wt% residual inorganics) x Chromatographic Purity/100].
- Purity factor does not include adjustment for chiral and/or isotopic purity.

¹ Validated analytical method.

Spectral and Physical Data

HPLC/UV



Column: Prodigy ODS 3, 5 µm, 4.6 x 250 mm
Mobile Phase: A.: Acetonitrile
 B.: 0.1% Phosphoric acid
Gradient Program:

Time (mins)	%A	%B
0.0	5	95
20.0	15	85
20.1	5	95

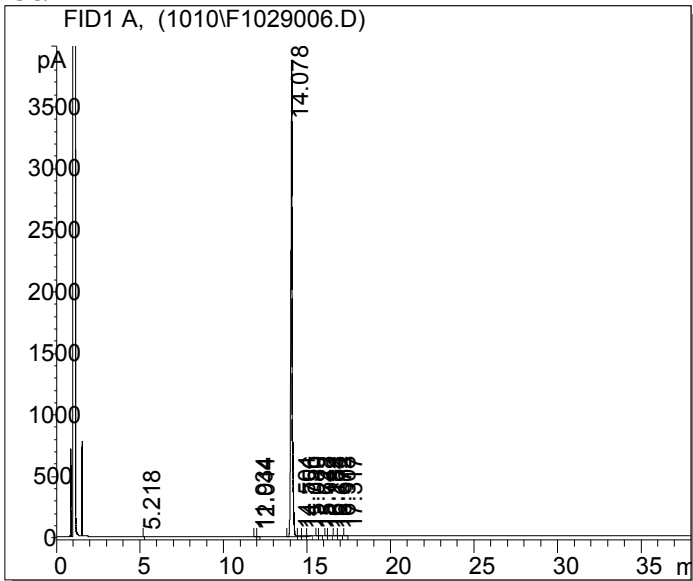
Flow Rate: 1.5 mL/min
Wavelength: 230 nm

Data File Name: S:\HPLC\HPLC3\2010\LC31110\P1101015.D
Instrument: LC#3
Sample Name: FC102110-01
Acquired: November 01, 2010

Peak #	Ret Time	Area	Height	Area %
1	4.16	0.20	0.03	0.01
2	4.36	0.61	0.12	0.04
3	4.69	0.21	0.04	0.01
4	4.85	1.38	0.21	0.09
5	5.69	0.31	0.04	0.02
6	6.85	0.96	0.12	0.06
7	7.99	1549.04	155.34	99.65
8	9.85	1.41	0.19	0.09
9	11.75	0.40	0.04	0.03

Spectral and Physical Data (cont.)

GC/FID

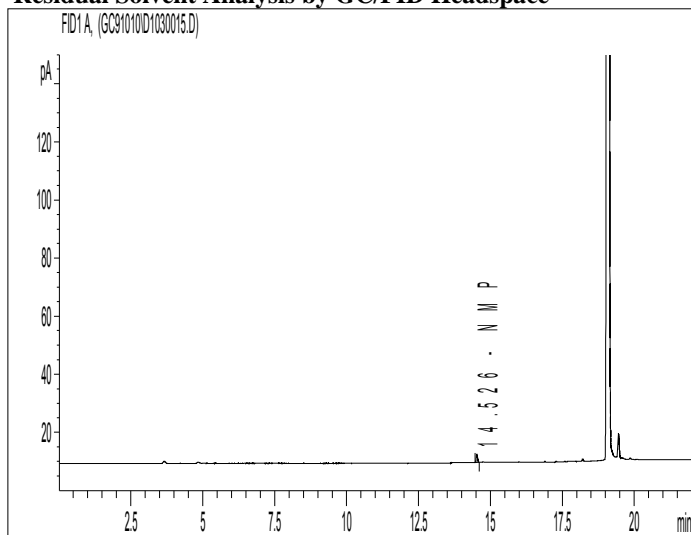


Column: DB-5ms, 30 m x 0.53 mm ID, 1.5 µm film thickness
Temp Program: 40°C to 200°C at 40°C/min
 200°C to 280°C at 5°C/min hold 18 min
Injector Temp: Cool-on-Column
Detector Temp: 325°C
Data File Name: S:\GC\GC6\2010\1010\F1029006.D
Instrument: GC#6
Sample Name: FC102110-01
Acquired: October 29, 2010

Peak #	Ret Time	Area	Height	Area %
1	5.22	0.40	0.15	0.00
2	11.93	1.41	0.31	0.01
3	12.04	1.86	0.35	0.01
4	14.08	23192.50	3860.88	99.60
5	14.50	10.45	1.09	0.04
6	14.76	7.86	0.71	0.03
7	15.08	7.04	0.89	0.03
8	15.63	2.43	0.47	0.01
9	15.74	3.48	0.43	0.01
10	16.18	12.74	2.53	0.05
11	16.28	25.24	3.21	0.11
12	16.67	9.84	1.42	0.04
13	16.91	9.03	1.22	0.04
14	17.32	0.89	0.17	0.00

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

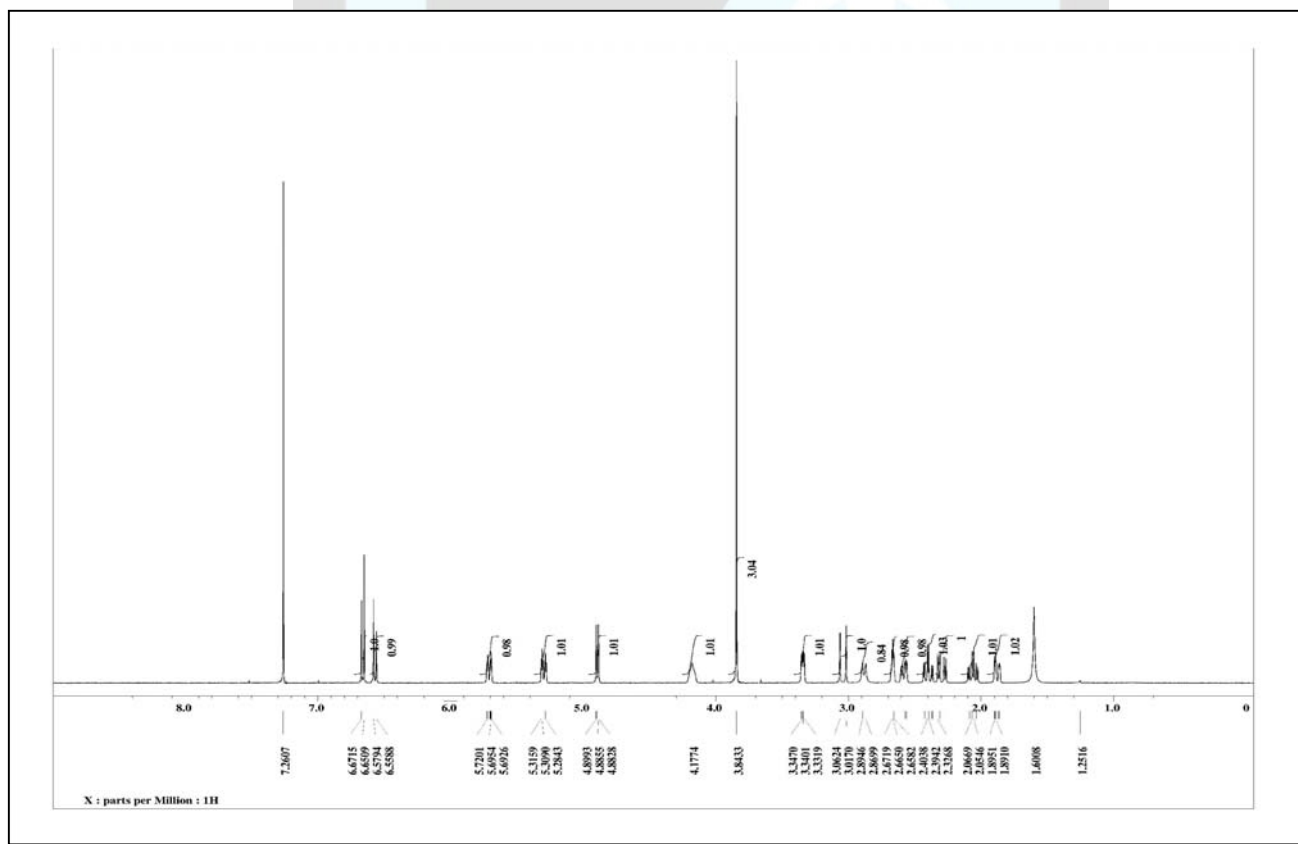
Data File Name: C:\CHEM32\1\DATA\GC91010\D1030015.D
Instrument: GC#9
Sample Name: FC102110-01
Acquired: October 30, 2010

Peak	Compound	Area	Weight %
1	NMP	NA	NA
Total			ND

ND - None Detected

¹H NMR

Instrument: JEOL ECS 400
Solvent: Chloroform-D



Spectral and Physical Data (cont.)

LC/MS

Column: Kinetex C18, 2.6 μ m, 2.1 x 50 mm

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

Gradient:	Time (min)	% A	% B
	0.0	5	95
	1.0	5	95
	5.0	90	10
	8.0	90	10
	8.5	5	95
	16.0	5	95

Flow Rate: 0.4 mL/min

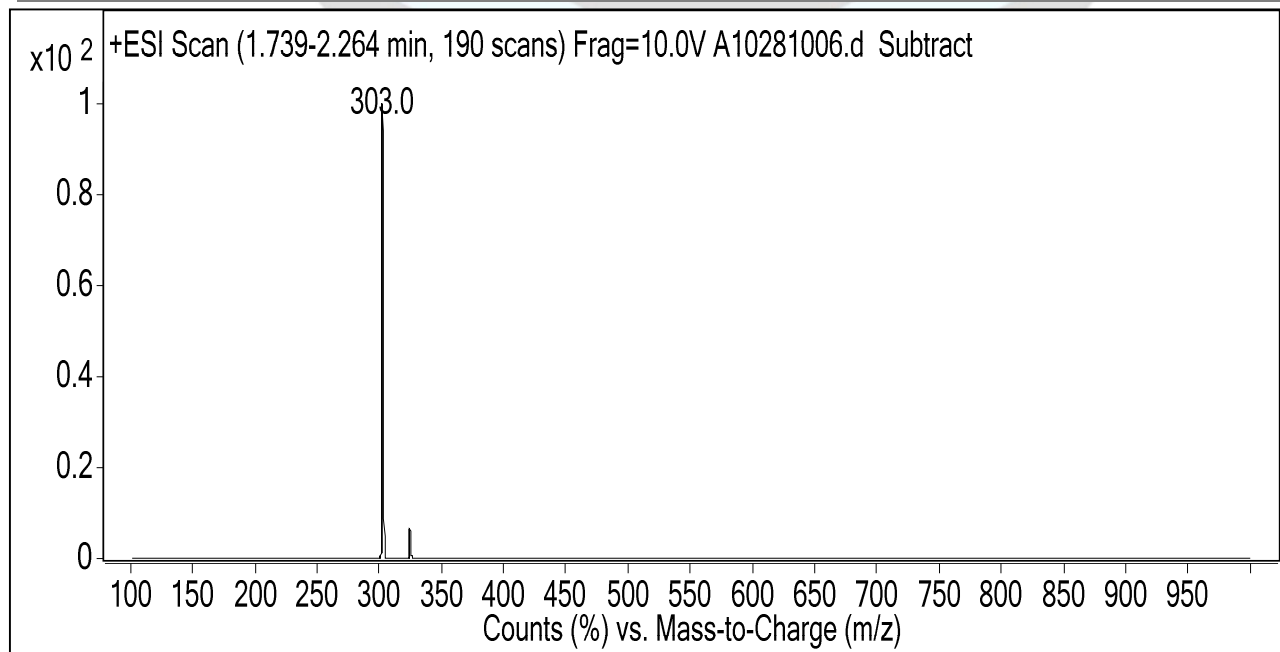
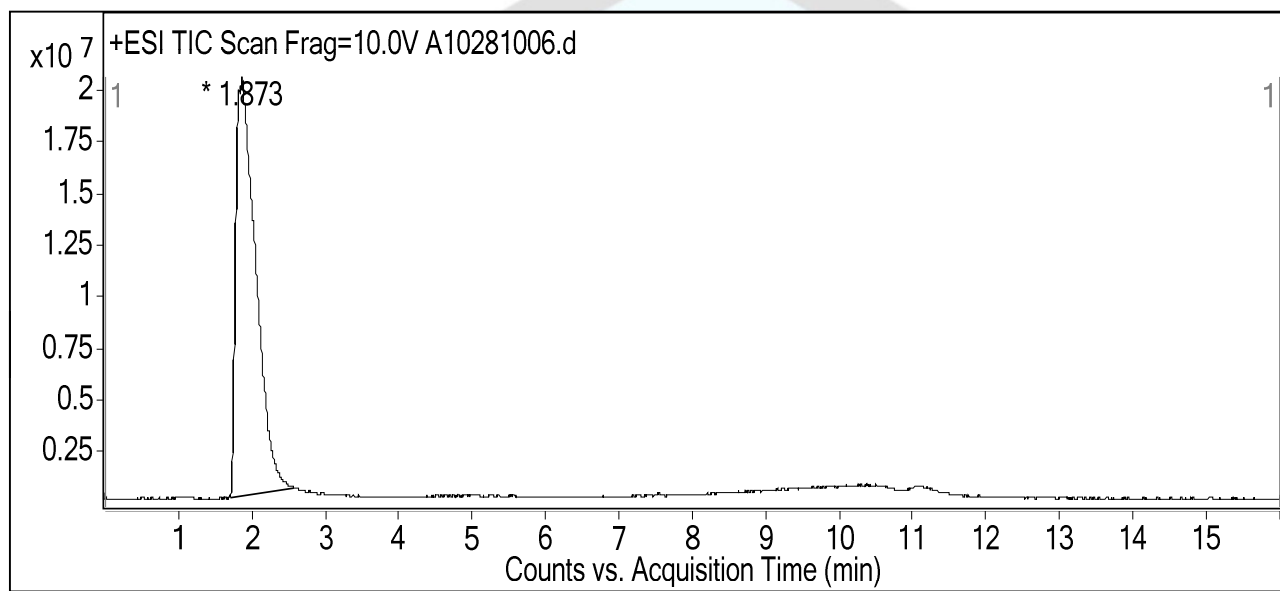
Scan Range: 100-1000 amu

Ionization: Electrospray, Positive Ion

Instrument: LC/MS/MS

Sample Name: FC102110-01

Acquired: October 28, 2010



Spectral and Physical Data (cont.)

Isotopic Purity by LC/MS SIM Analysis

Column: Kinetex C18, 2.6 μ m, 2.1 x 50 mm

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

Gradient:

Time (min)	% A	% B
0.0	5	95
1.0	5	95
5.0	90	10
8.0	90	10
8.5	5	95
16.0	5	95

Flow Rate: 0.4 mL/min

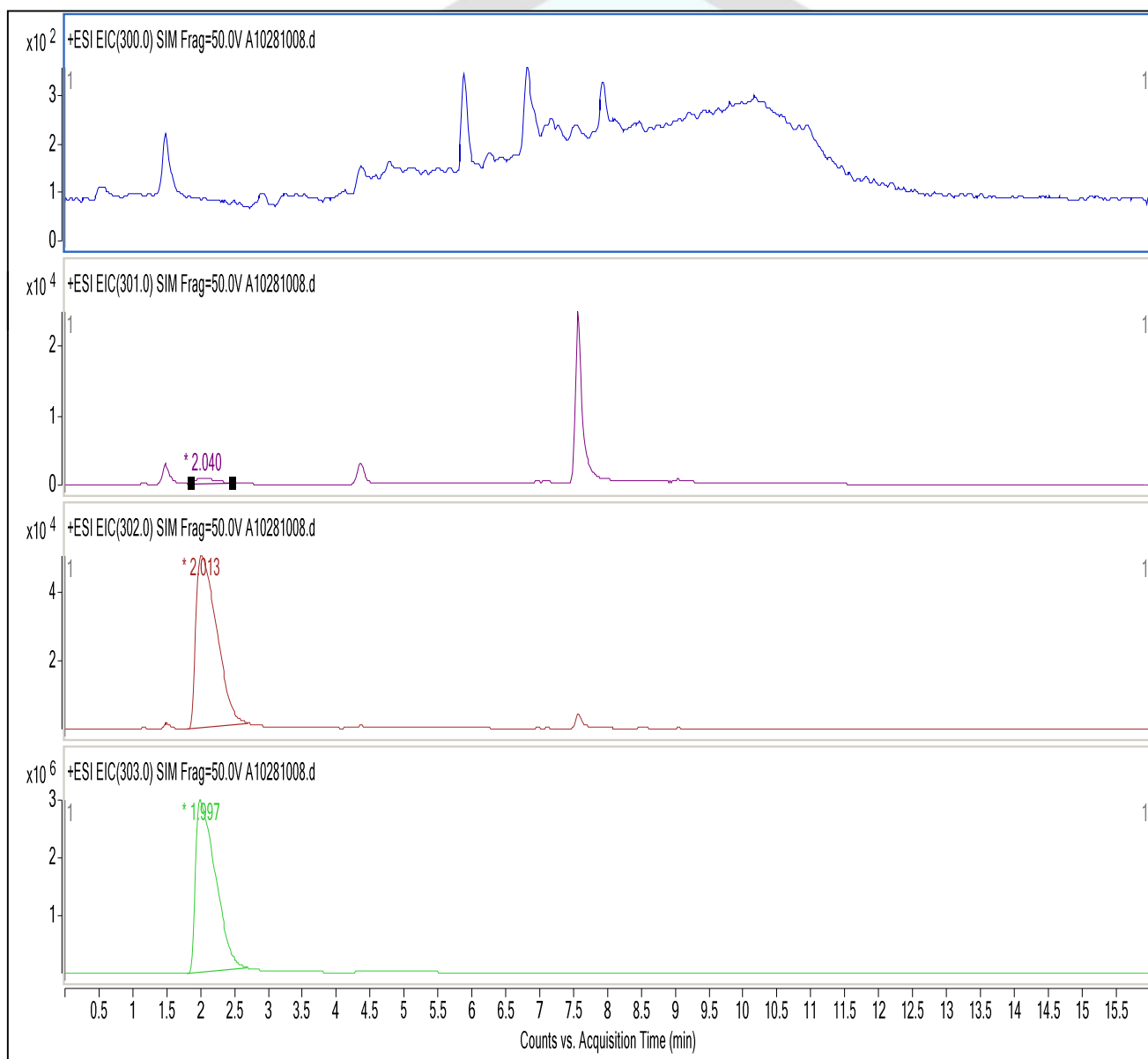
Scan Range: 300 - 303 amu

Data File Name: A10281006.d

Instrument: LC/MS/MS

Sample Name: FC102110-01

Acquired: October 28, 2010



Stability

Short term stability studies have been performed under accelerated conditions for a period of up to four weeks. 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 (C-041, Codeine-D₆) is listed below.

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

Transport/Shipping: Stability data supports transport of this product at ambient conditions.

Short Term Storage: Stability data supports short term storage up to 12 months at Refrigerate conditions.

Long Term Stability: Long term stability has been assessed for Freezer storage (-10 °C to -25 °C) conditions. Stability of a minimum of 60 months has been established through real-time stability studies.

COA Revision History

Revision No.	Date	Reason for Revision
00	September 15, 2012	Initial version
01	April 28, 2015	Updated Safety Section from "Flammable, Poison" to "Danger. See Safety Data Sheet"
		Added minimum sample size and MS application statements to first page.
		Updated Stability section.