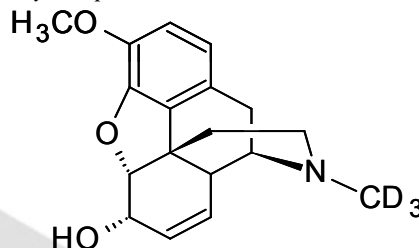


# Certificate of Analysis

## Codeine-D<sub>3</sub>

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

<b>Catalog Number:</b>	C-005	<b>Safety:</b>	Flammable, Poison
<b>Solution Lot:</b>	FE080612-02		
<b>Expiration Date:</b>	August 2017		
<b>Solvent:</b>	Methanol		
<b>Volume per Ampule:</b>	Not less than 1 mL		
<b>Storage:</b>	Store unopened in freezer.		
<b>Shipping:</b>	Ambient. See Stability Section.		
<b>Intended Use:</b>	For R&D/ analytical purposes only. Not suitable for human or animal consumption.		
<b>Regulatory:</b>	USDEA Exempt   Canadian TK# 61-17		

- 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.

Component	Solution Purity	Certified Concentration
Codeine-D <sub>3</sub>	99.5%	100.0 ± 0.6 µg/mL
<ul style="list-style-type: none"> <li>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.</li> <li>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.</li> <li>Concentration is corrected for chromatographic purity, residual water, residual solvents and residual inorganics.</li> </ul>		

### Solution Standard Verification and Homogeneity

Standard Solution	Lot Number	Verified Concentration (µg/mL)		%RSD - Homogeneity	
		Actual Results	Acceptance Criteria	Actual Results	Acceptance Criteria
New Lot	FE080612-02	98.8	± 3%	0.7	≤ 3%
Previous Lot	FE102308-01	99.7	± 3%		
<ul style="list-style-type: none"> <li>Concentration is verified through multiple analyses and is calculated as the average of multiple analyses compared to an independently prepared calibration solution.</li> <li>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.</li> </ul>					

### Traceability

<ul style="list-style-type: none"> <li>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.</li> <li>Concentration is verified against an independently prepared calibration solution gravimetrically prepared using balances calibrated to NIST.</li> <li>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.</li> </ul>
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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.



*Lara Sparks*  
Lara Sparks, Quality Assurance Director

August 29, 2012

Date

### Standard Solution Assay Parameters

**Analysis Method:** UV/Vis  
**Wavelength:** 230 nm  
**Slit Width:** 1.0 nm  
**Response:** 0.5 s

### Calibration Curve

**Calibration Curve:** Linear Regression  
**Number of Points:** 4  
**Linearity (r):** 0.999

### Neat Material Data

**Compound Name:** Codeine-D<sub>3</sub>  
**Compound Lot:** FC102110-01

**Chemical Formula:** C<sub>18</sub>H<sub>18</sub>D<sub>3</sub>NO<sub>3</sub>  
**CAS Number:** 70420-71-2  
**Molecular Weight:** 302.35

#### Neat Material Characterization Summary

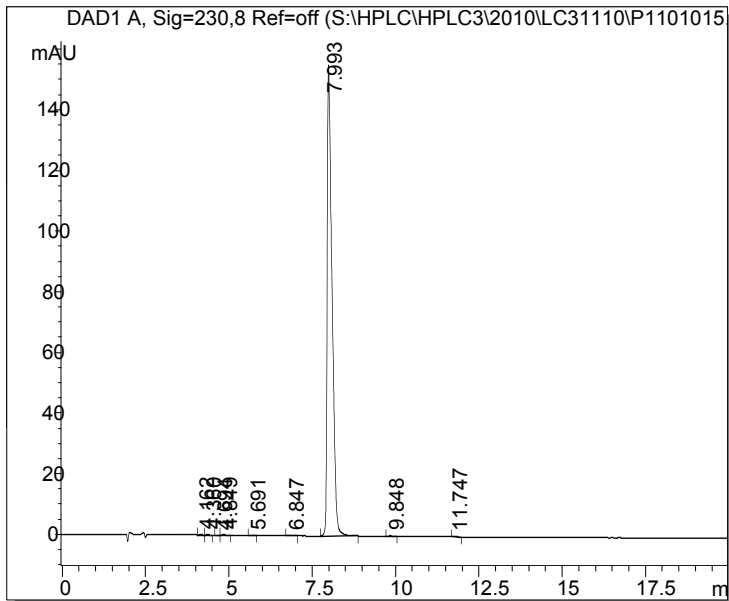
Analytical Test	Method	Results
Primary Chromatographic Purity by HPLC/PDA Analysis	SP10-0102	99.6%
Secondary Chromatographic Purity by GC/FID Analysis	SP10-0101	99.6%
Identity by LC/MS Analysis	SP10-0107	Consistent with Structure
Isotopic Purity by LC/MS SIM Analysis	SP10-0107	0.00% D <sub>0</sub> vs D <sub>3</sub>
		0.00% D <sub>0</sub>   1.72% D <sub>2</sub>
		0.03% D <sub>1</sub>   98.26% D <sub>3</sub>
Identity by <sup>1</sup> H-NMR Analysis	USP <761>, SP10-0116	Consistent with Structure
Residual Solvent Analysis by GC/FID Headspace	AM1087 <sup>1</sup>	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.

<sup>1</sup> Validated analytical method.

*Spectral and Physical Data*

**HPLC/PDA**



**Column:** Prodigy ODS 3 5μ, 4.6 x 250 mm  
**Mobile Phase:** A: Acetonitrile B: 0.1% H<sub>3</sub>PO<sub>4</sub>  
**Gradient**

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

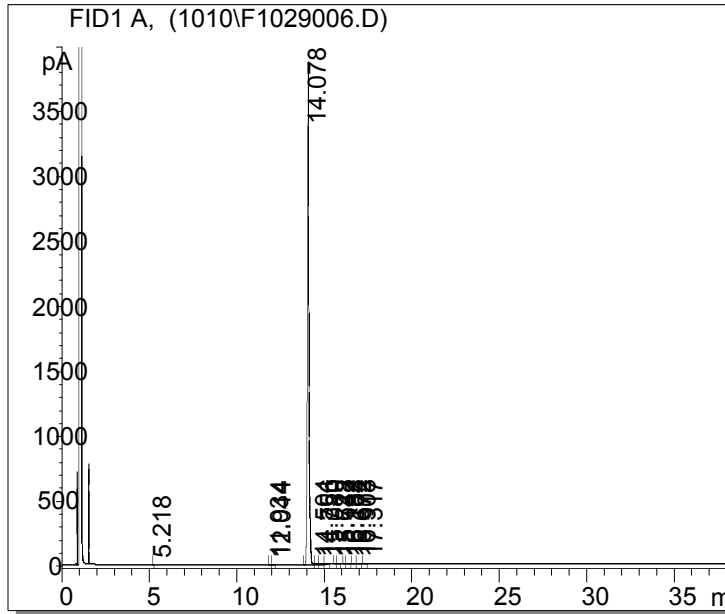
**Program:**  
**Flow Rate:** 1.5 mL/min  
**Wavelength:** 230 nm

**Data File Name:** S:\HPLC\HPLC3\2010\LC31110\P1101015.D  
**Operator:** TNT  
**Instrument:** LC#3  
**Sample Name:** FC102110-01  
**Method File:** RMC017-2.M  
**Acquired:** November 1, 2010 5:47 PM

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

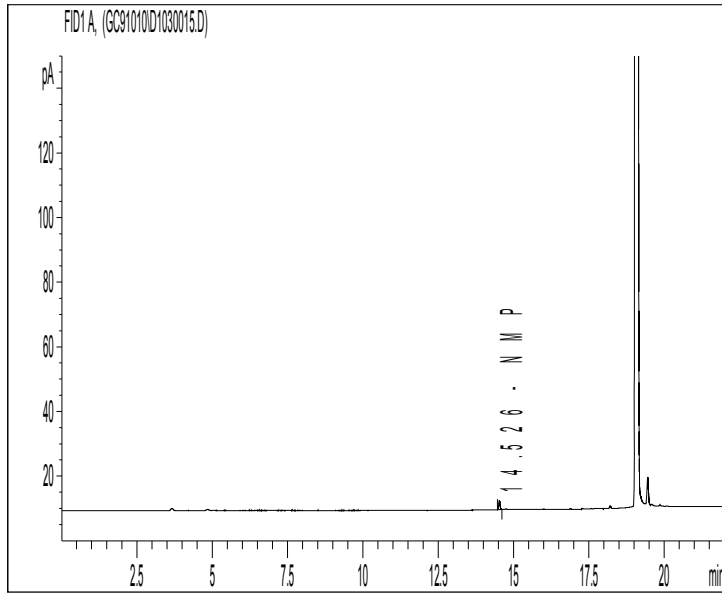


**Column:** DB-5ms, 30 m x 0.53 mm ID, 1.5 µm film thickness  
**Temp Program:** 40°C to 200°C at 40°C/min  
 200°C to 280°C at 5°C/min (hold 18 min)  
**Injector Temp:** Cool-on-Column  
**Detector Temp:** 325°C  
**Data File Name:** S:\GC\GC6\2010\1010\F1029006.D  
**Operator:** RPC  
**Instrument:** GC#6  
**Sample Name:** FC102110-01  
**Method File:** AM1045.M  
**Acquired:** October 29, 2010 1:34 PM

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

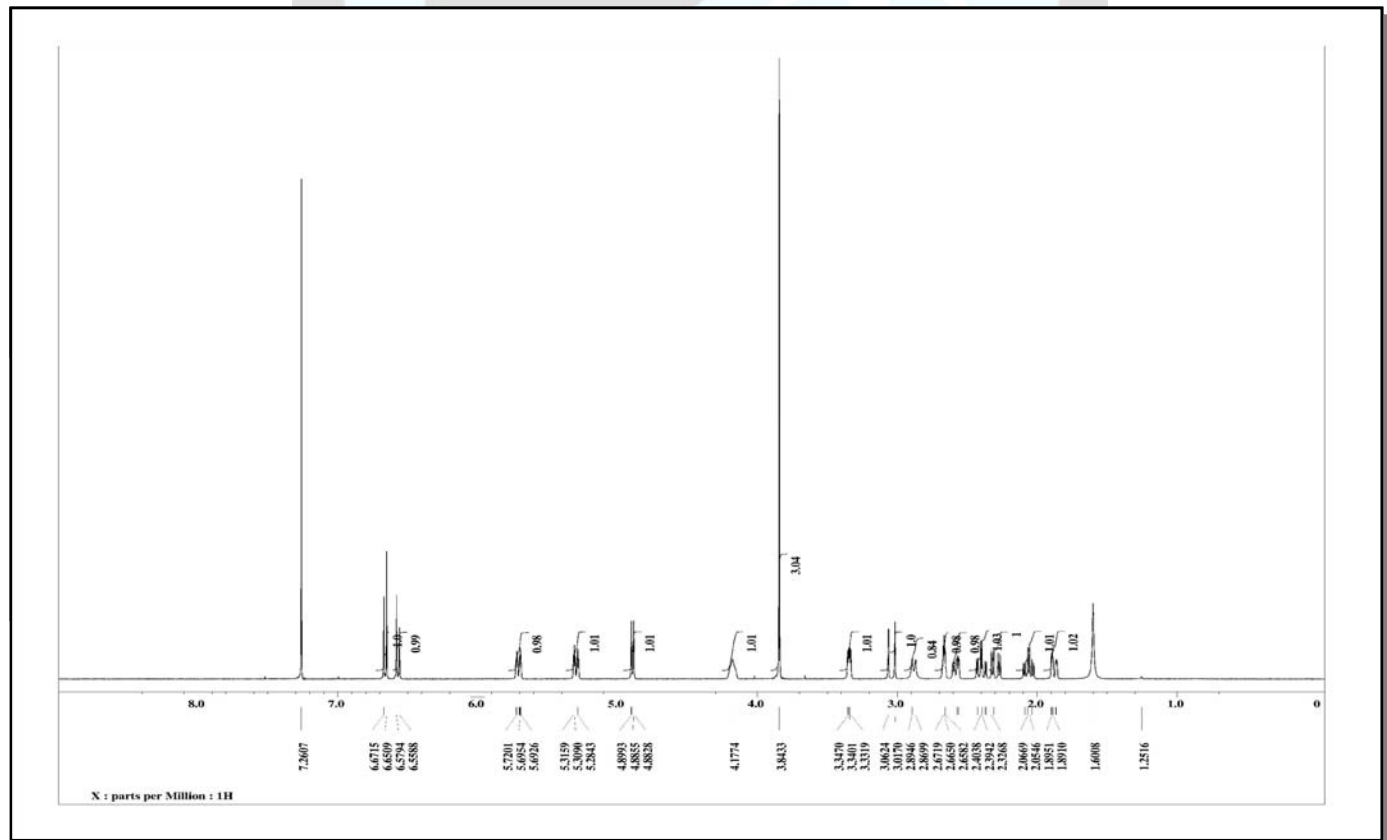
**Data File Name:** C:\CHEM32\1\DATA\GC91010\D1030015.D  
**Operator:** RPC  
**Instrument:** GC#9  
**Sample Name:** FC102110-01  
**Acquired:** October 30, 2010 4:46 PM

Peak	Compound	Area	Weight %
1	NMP	NA	NA
<b>Total</b>			<b>ND</b>

ND - Not Detected

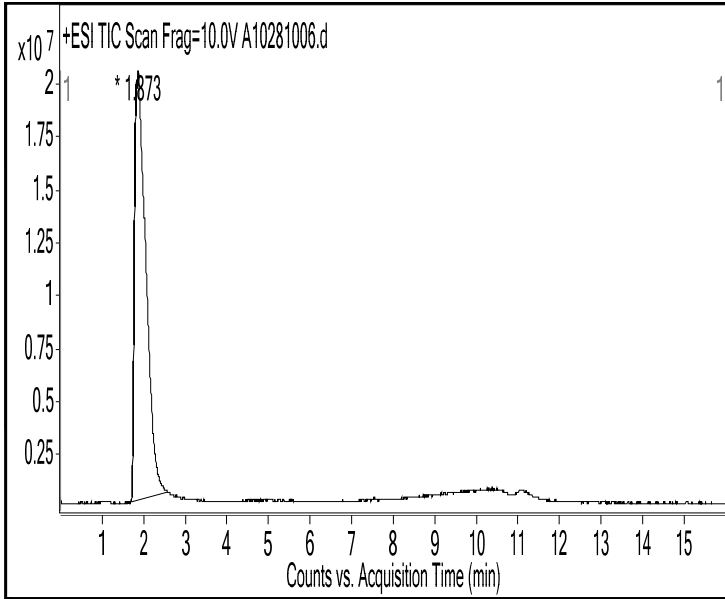
**<sup>1</sup>H NMR**

**Instrument:** JEOL ECS 400  
**Solvent:** Chloroform-D



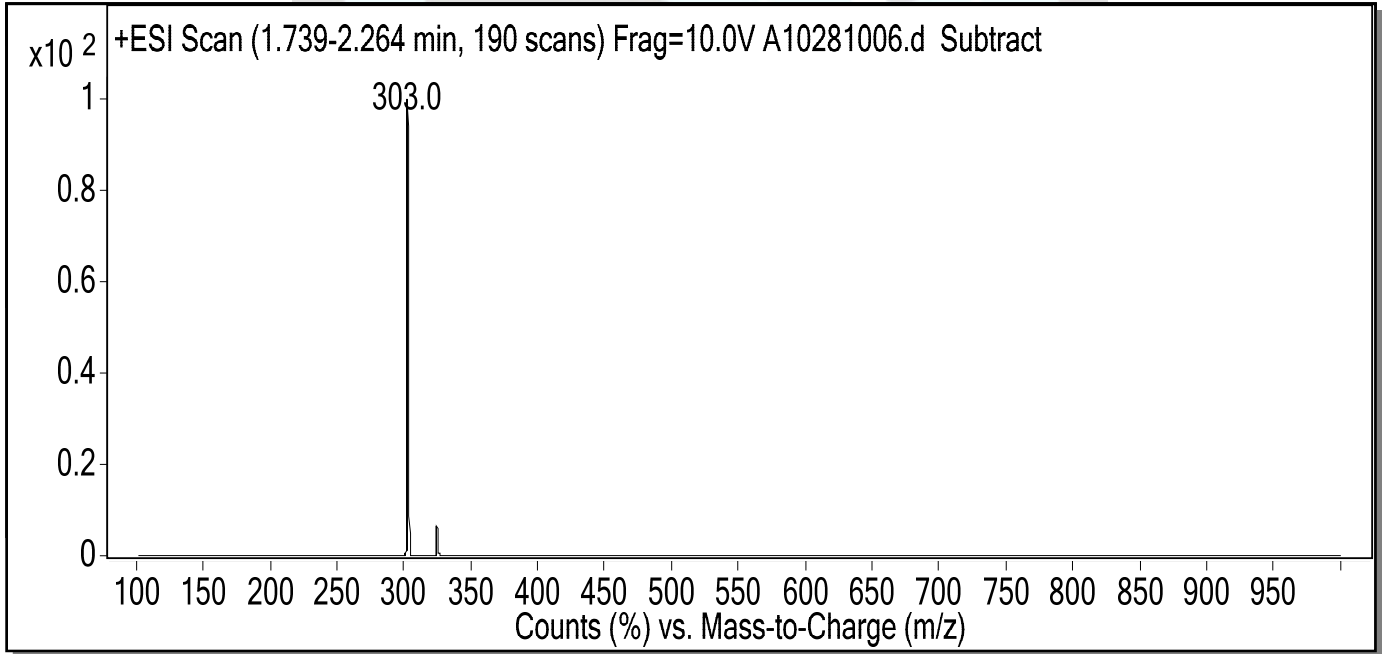
*Spectral and Physical Data (cont.)*

**LC/MS**



**Column:** Kinetex 2.6 $\mu$  C<sub>18</sub>, 2.1 x 50 mm  
**Mobile Phase:** Acetonitrile::0.1% Formic acid  
(5::95 to 90::10 at 5 mins to 5::95 at 8.5 mins)  
**Flow Rate:** 0.4 mL/min  
**Scan Range:** 100-1000 amu  
**Ionization:** Electrospray, Positive Ion

**Data File Name:** A10281006.d  
**Operator:** JDC  
**Instrument:** LC/MS/MS  
**Sample Name:** FC102110-01  
**Method File:** genmsscan4.m  
**Acquired:** October 28, 2010 12:40 PM

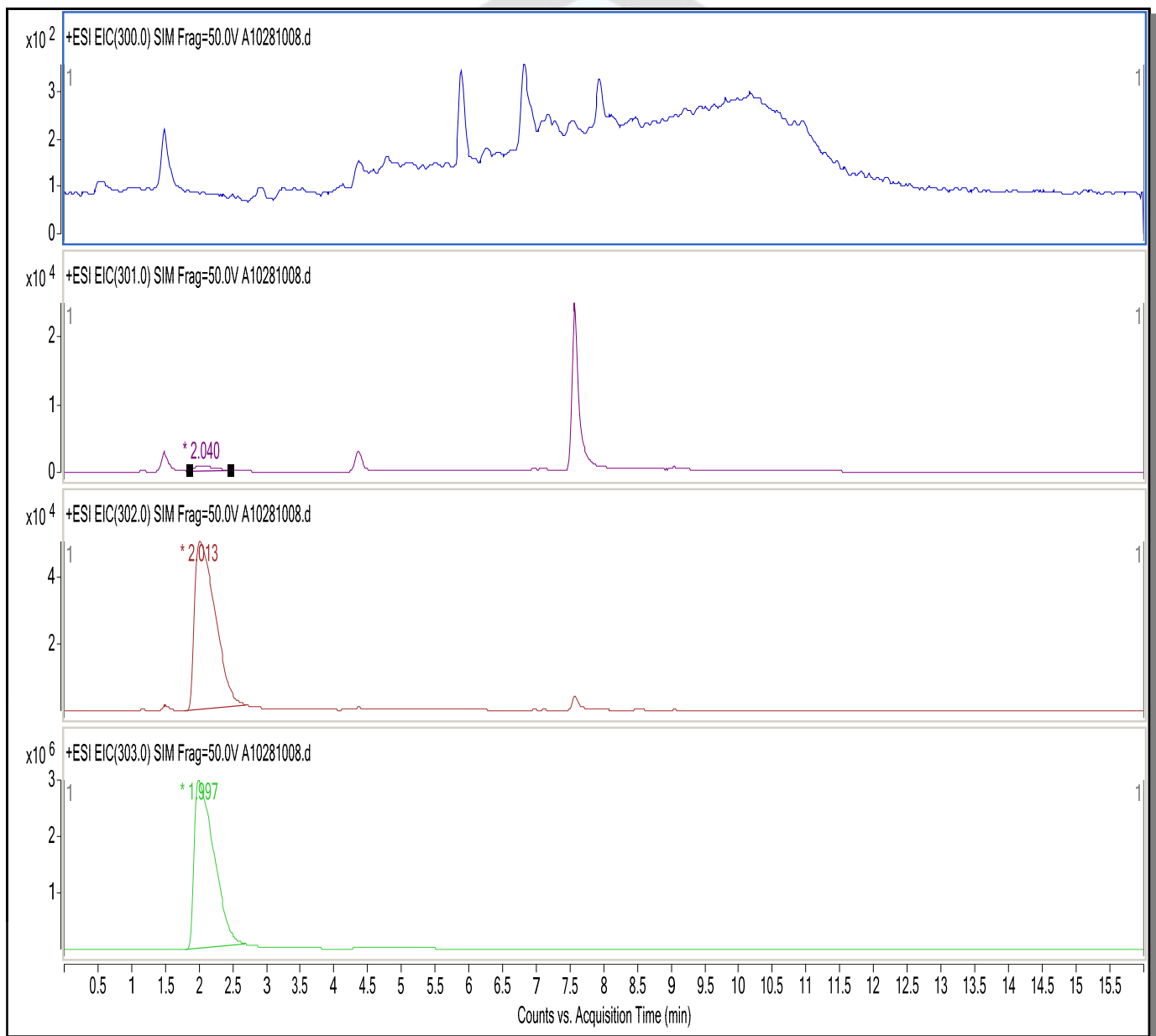


*Spectral and Physical Data (cont.)*

**Isotopic Purity by LC/MS SIM Analysis**

**Column:** Kinetex 2.6 $\mu$  C<sub>18</sub>, 2.1 x 50 mm  
**Mobile Phase:** Acetonitrile::0.1% Formic acid  
(5::95 to 90::10 at 5 mins to 5::95 at 8.5 mins)  
**Flow Rate:** 0.4 mL/min  
**Scan Range:** 100-1000 amu  
**Ionization:** Electrospray, Positive Ion

**Data File Name:** A10281006.d  
**Operator:** JDC  
**Instrument:** LC/MS/MS  
**Sample Name:** FC102110-01  
**Method File:** genmsscan4.m  
**Acquired:** October 28, 2010 12:40 PM



## Stability

**Short Term Stability :** A summary of accelerated stability findings for a related product (Codeine) is listed below.

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

**Transport/Shipping :** Stability data supports transport of this product at MKT not exceeding 40 °C over a period of one week.

