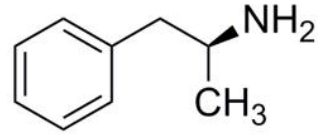
Certified Reference Material - Certificate of Analysis

S(+)-Amphetamine, Primary Measurement Standard

(+)-1-Phenyl-2-aminopropane

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

Product No.: A-008-1ML
Lot No.: FE05241804
Description of CRM: S(+)-Amphetamine in Methanol (Solution)
Expiration Date: June 2023 See Section "Stability Assessment".
Storage: Store unopened in freezer (-10 °C to -25 °C).
Shipping: Ambient. See Section "Stability Assessment".
Chemical formula: $C_9H_{13}N$
CAS No.: 51-64-9
Regulatory: USDEA Exempt | Canadian TK # 61-989



Analyte	Certified Concentration ± associated uncertainty U, u=k*u (k=2)
S(+)-Amphetamine	1.000 ± 0.006 mg/mL

Metrological traceability: Traceable to the SI and higher order standards from NIST through an unbroken chain of comparisons. See "Details on metrological traceability" on page 2.

Measurement method: The certified value is calculated from high precision weighing of thoroughly characterized starting material. See "Details about certification process" on page 2.

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.

Minimum sample size: 1 µL for quantitative applications

Instructions for handling and correct use: Concentration is corrected for chromatographic purity, residual solvents and residual inorganics. No adjustment required before 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.

Health and safety information: Danger. Please refer to the Safety Data Sheet for detailed information about the nature of any hazard and appropriate precautions to be taken.

Accreditation: Cerilliant Corp. is accredited by the US accreditation authority ANAB as registered reference material producer AR-1353 in accordance with ISO Guide 34 and registered testing laboratory AT-1352 according to ISO/IEC 17025.

Darron Ellsworth, Quality Assurance Manager

August 21, 2018
Issue Date

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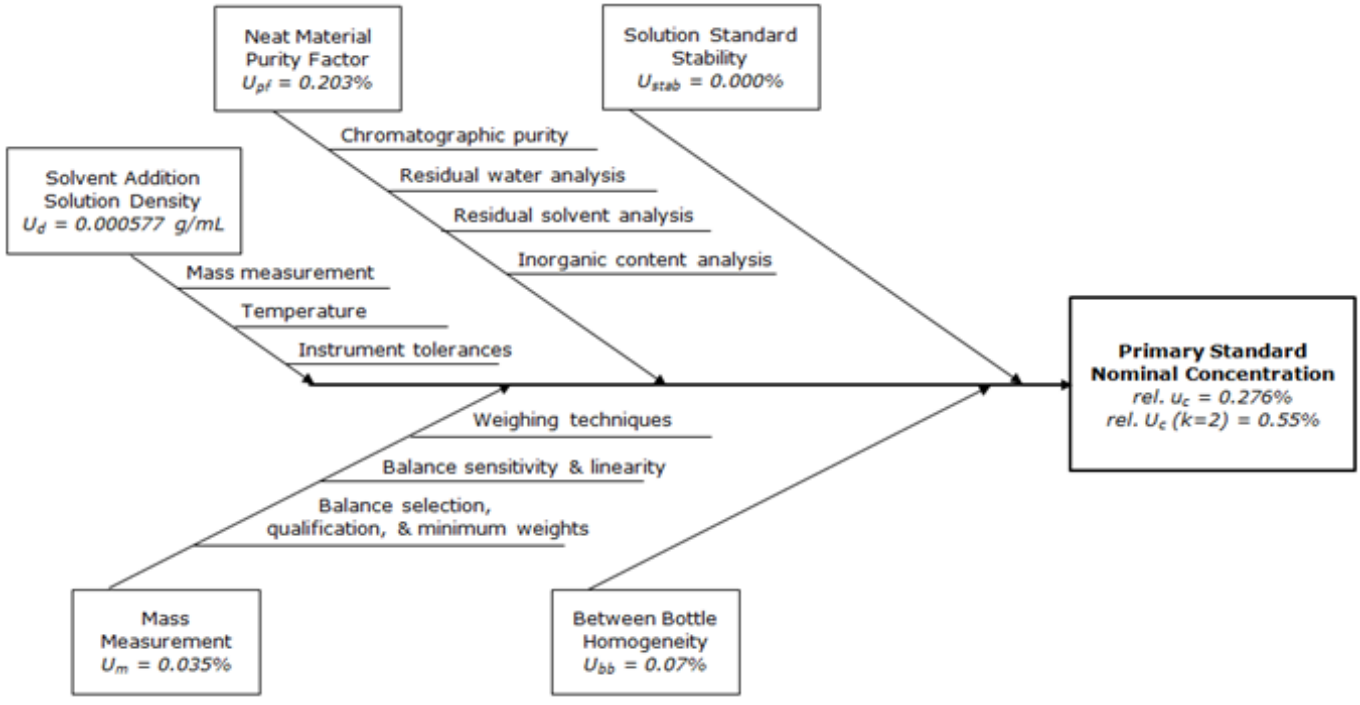
Packaging: 2 mL amber USP Type 1 glass ampoule containing not less than 1 mL of certified solution. Ampoules are overfilled to ensure a minimum of 1 mL volume can be transferred when using a 1mL Class A volumetric pipette.

Details on starting materials: Each raw material utilized has been identified and thoroughly characterized through the use of multiple analytical techniques and is assigned a Mass Balance Purity Factor. Spectral data is provided on subsequent pages of this CoA.

Certificate of Origin: Cerilliant Corporation certifies no material of animal origin (BSE/TSE) was used in the preparation of this product. This material was manufactured in the USA.

Associated uncertainty:

The uncertainty has been calculated by statistical analysis of all aspects of our production system and incorporated uncertainty of the mass balance purity factor, material density, balance, weighing technique, and homogeneity. Uncertainty components of the gravimetrically prepared Primary Standard concentration are shown in the figure below. Uncertainty is expressed as an expanded uncertainty in accordance with ISO Guide 34 at the approximate 95% confidence interval using a coverage factor of k=2. Uncertainty contribution from neat material homogeneity was established to be negligible through establishment of process controls and verification of the control process. Stability uncertainty was determined to be negligible by regression analysis.



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Details on metrological traceability:

- 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.
- Fill volume to predetermined specifications is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- The density and material Mass Balance Purity Factor of each raw material is traceable to the SI and higher order reference materials through mass measurement and instrument qualification and calibrations.

Details about certification process:

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 Standard as defined by ISO and is traceable to the SI and higher order standards through an unbroken chain of comparisons.

- Nominal concentration is calcuated based on: the actual mass; Mass balance purity factor of the analyte(s); measured mass of the solution; and the density of the pure diluent at 20°C.
- 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.
- Additional certification information available upon request.

Solution Standard Verification

Concentration accuracy and within- and between-bottle homogeneity areanalytically verified against an independently prepared calibration solution and to the prior lot.

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		**Calibration Curve**	
Analysis Method:	GC/FID	**Calibration Curve:**	Linear Regression
Column:	DB-5ms, 30 m x 0.53 mm ID, 1.5 µm film thickness	**Number of Points:**	4
		Linearity (r) :	1.000
Temp Program:	60°C to 260°C at 20°C/min hold 1 min		
Injector Temp:	Cool-on-Column		
Detector Temp:	325°C		

		Verified Concentration (mg/mL)	**%RSD - Homogeneity**
Standard Solution	**Lot Number**	**Actual Results**	**Actual Results**
New Lot	FE05241804	0.988	0.4
Previous Lot	FE01261601	0.973	0.3

- 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.

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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:	S(+)-Amphetamine	**Chemical Formula:**	$C_9H_{13}N$
Material Lot:	FC05061601	**CAS Number:**	51-64-9
		Molecular Weight:	135.21

Material Characterization Summary

Analytical Test	Method	Results
Primary Chromatographic Purity by GC/FID Analysis	SP10-0101	> 99.9%
Secondary Chromatographic Purity by HPLC/UV Analysis	SP10-0102	99.8%
Chiral Purity by GC/FID Analysis	AM1098	93.2% ee
Identity by GC/MS Analysis	SP10-0107	Consistent with Structure
Identity by ^{1}H-NMR Analysis	USP <761>, SP10-0116	Consistent with Structure
Residual Solvent Analysis by GC/FID Headspace	AM1087 [1]	None Detected
Residual Water Analysis by Karl Fischer Coulometry	AM1346 [1]	Below Quantitation Limit
Inorganic Content by Microash Analysis	SP10-0135	< 0.2%
Mass Balance Purity Factor		99.95%

[1] Validated analytical method

- 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 purity method was selected to optimize resolution of impurities while minimizing degradation of the analyte. Secondary purity methods with orthogonal detector capabilities from the primary purity method are used as controls to confirm an accurate purity value.
- 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.

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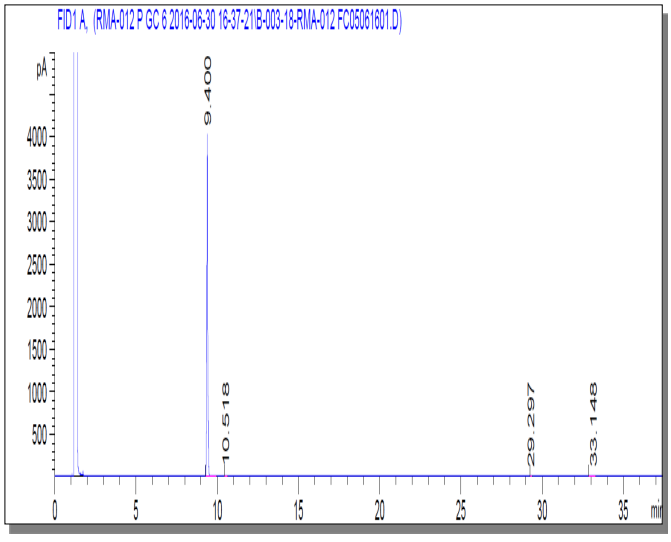
Spectral and Physical Data

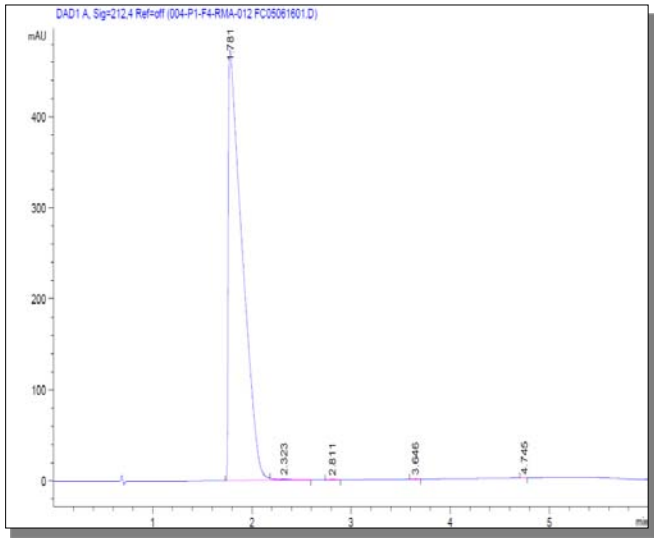
GC / FID



Column:	DB-5ms, 30 m x 0.53 mm ID, 1.5 µm film thickness
Temp Program:	40°C to 80°C at 40°C/min 80°C to 175°C at 5°C/min 175°C to 300°C at 10°C/min hold 5 min
Injector Temp:	Cool-on-Column
Detector Temp:	325°C
Sample Name:	FC05061601
Acquired:	June 30, 2016

Peak #	Ret Time	Area %
1	9.40	99.93
2	10.52	0.01
3	29.30	0.03
4	33.15	0.03

HPLC / UV



Column:	Ascentis Express Phenyl-Hexyl, 2.7 µm, 3.0 x 100 mm
Mobile Phase:	A: Methanol B: 0.1% Phosphoric acid

Gradient:

Time (min)	% A	% B
0.0	20	80
3.0	40	60
4.0	40	60
4.1	20	80

Flow Rate:	0.6 mL/min
Wavelength:	212 nm
Sample Name:	FC05061601
Acquired:	June 27, 2016

Peak #	Ret Time	Area %
1	1.78	99.78
2	2.32	0.15
3	2.81	0.04
4	3.65	0.02
5	4.75	0.00

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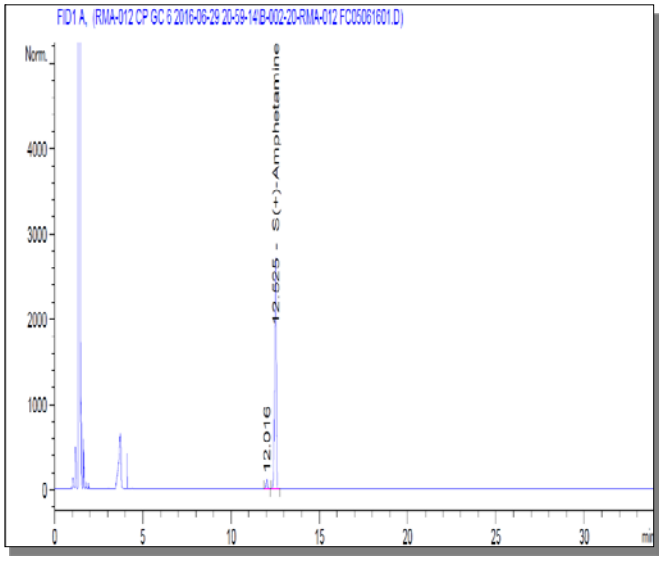
Spectral and Physical Data (cont.)

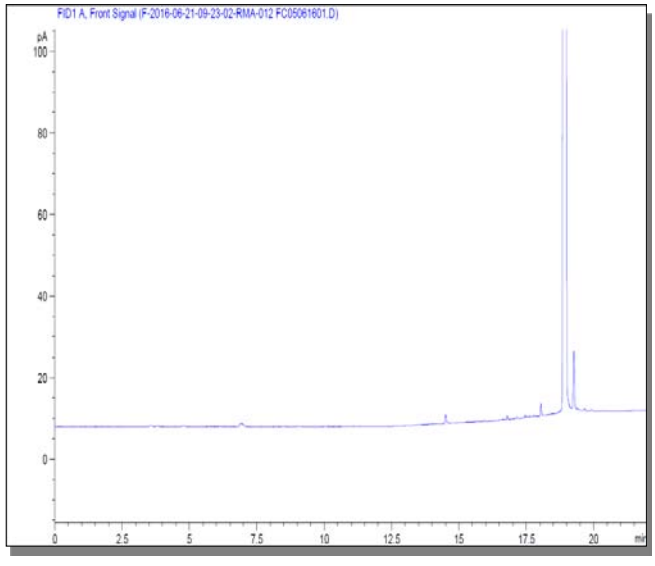
Chiral Purity by GC/FID



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 260°C at 2°C/min
Injector Temp:	Cool-on-Column
Detector Temp:	325°C
Sample Name:	FC05061601
Acquired:	June 29, 2016

Peak #	Ret Time	Area %	
1	12.02	3.50	R(-)-Amphetamine
2	12.53	96.50	S(+)-Amphetamine

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
Sample Name:	FC05061601
Acquired:	June 21, 2016

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

ND- None Detected

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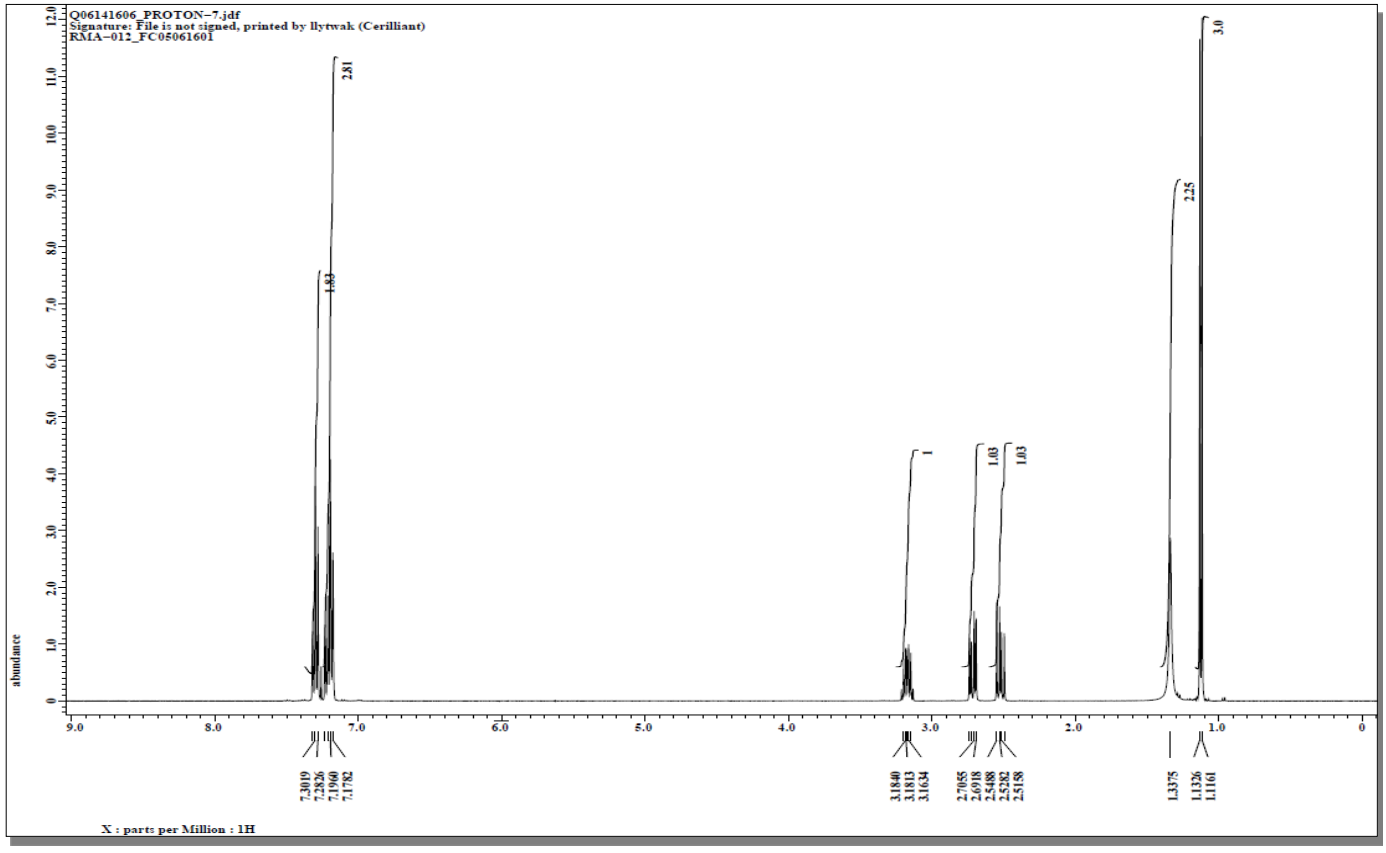
Spectral and Physical Data (cont.)

^{1}H NMR

Instrument: JEOL ECS 400
Solvent: Chloroform-D



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Spectral and Physical Data (cont.)

GC / MS

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Compound Name          : S(+)-Amphetamine/TFAA
Lot Number             : FC05061601
Instrument             : Agilent GCMS
Operator               : ECM(SGIUFFRE)
Date Reported          : Thu Jun 16 09:50:17 2016
Column Type            : DB-5ms, 30m x 0.25mm ID, 0.25um film thickness
Temp. Program          : 50°C to 300°C @ 10°C/min, hold for 4 minutes
Injector Temp.         : Cool on-column
Carrier Gas            : Helium
Flow Rate (mL\min)     : 0.80 mL/min
Transfer Line Temp.    : 280°C
Scan Range             : 35-600
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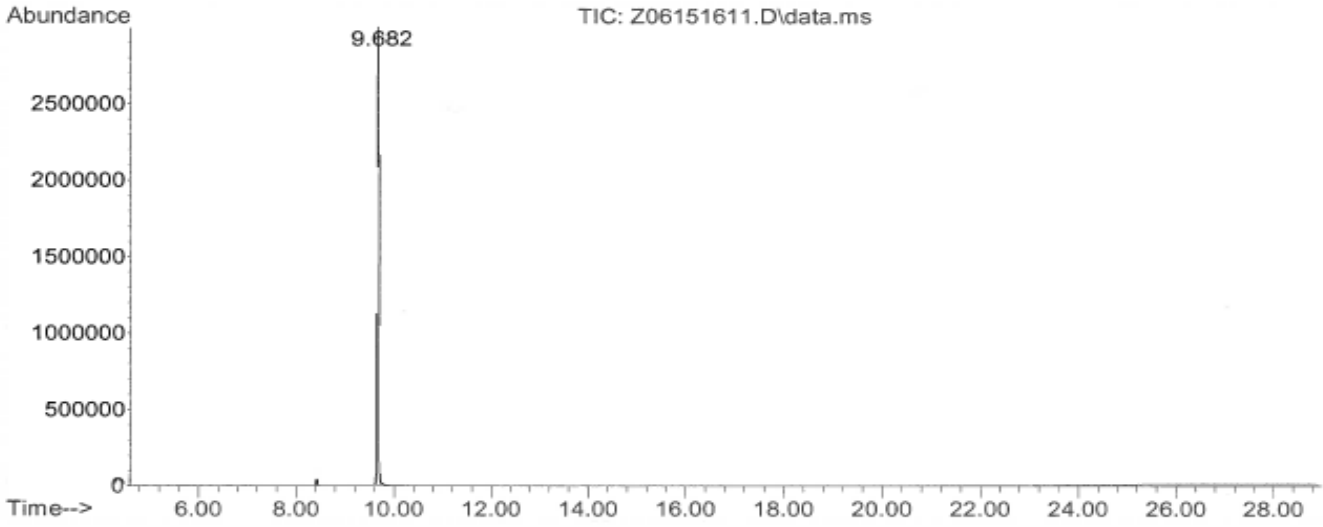
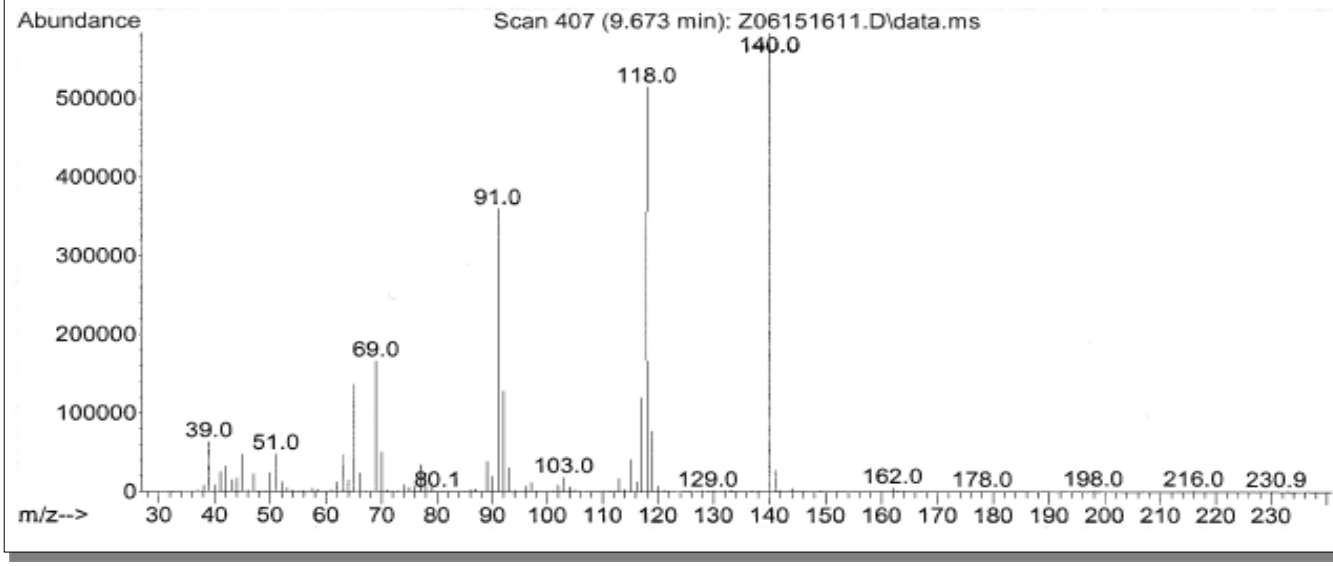
Total Ion Chromatogram



Mass Spectrum



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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 (A-016, (±)-Amphetamine-D_{11}) 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 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 60 months has been established through real-time stability studies.*

Commutability

This standard is a solution of a pure substance in an organic solvent and is a Primary Standard. This Primary Standard is suitable for use in the preparation of calibrators and/or controls in any biological matrix. This standard is not in a biological matrix and therefore commutability to methods or standards in biological matrices does not apply.

COA Revision History

Revision No.	Date	Reason for Revision
00	August 21, 2018	Initial version.

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