

Certified Reference Material - Certificate of Analysis

(±)-Amp	hetamine, Primary Measurement Standard	Cerilliant Quality
	1-Phenyl-2-aminopropane	ISO 17034
Product No.:	A-007-1ML	ISO/IEC 17025
Lot No.:	FE01202014	ISO 13485
Description of CRM:	(±)-Amphetamine in Methanol (Solution)	150 14001
Expiration Date:	February 2025 See Section "Stability Assessment".	130 14001
Storage:	Store unopened in freezer (-10 °C to -25 °C).	ISO 9001
Shipping:	Ambient. See Section "Stability Assessment".	
Chemical formula:	C ₉ H ₁₃ N	$\mathbb{N}H_2$
CAS No.:	300-62-9	γ
Regulatory:	USDEA Exempt Canadian TK # 61-988	ĊН₃

Analyte		Certified Concentration \pm associated uncertainty U, $u=k*u$ (k=2)
(±)-Ampheta	mine	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 characterized star page 2.	e is calculated from high precision weighing of thoroughly ting material. See "Details about certification process" on
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 μ L for quantitati	ive applications
Instructions for handling and correct use: Health and safety	Concentration is of solvents, and resi Users should quar laboratory practic concentration. Eac Danger. Please re the nature of any	corrected for chromatographic purity, residual water, residual dual inorganics. No adjustment required before use. ntitatively transfer desired volume using established good es to spike into matrix or to dilute to the desired ch ampoule is intended for one-time use. fer to the Safety Data Sheet for detailed information about bazard and appropriate precautions to be taken
Accreditation:	cerilliant Corp. is registered referen and registered tes	accredited by the US accreditation authority ANAB as acce material producer AR-1353 in accordance with ISO 17034 sting laboratory AT-1352 according to ISO/IEC 17025.



Darron Ellsworth, Quality Assurance Manager

March 10, 2020

Issue Date

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 17034 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.



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 17034, 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 calculated 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 are analytically 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 μ m film thickness	Number of Points:	4
Injector Temp:	Cool-on-Column		1.000
Detector Temp:	325°C		

		verified Concentration (mg/mL)	%RSD - Homogeneity	
Standard	Lot Number	Actual Besults	Actual Posults	
Solution	Lot Number	Actual Results	Actual Results	
New Lot	FE01202014	0.985	0.7	
Previous Lot	FE04161901	0.982	0.7	

• 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: Material Lot:	(±)-Amphetamine FC09101802	Chemical Form CAS Number: Molecular Weig	ula: C ₉ H ₁₃ N 300-62-9 ght: 135.21
	Material Characte	erization Summary	
Analytical Test		Method	Results
Primary Chromatograph	ic Purity by GC/FID Analysis	SP10-0101	99.5%
Secondary Chromatographic Purity by HPLC/UV Analysis		SP10-0102	99.5%
Identity by GC/MS Analy	γsis	SP10-0105	Consistent with Structure
Identity by ¹ H-NMR Ana	lysis	USP <761>, SP10-0116	Consistent with Structure
Residual Solvent Analys	is by GC/FID Headspace	AM1087 ¹	None Detected
Residual Water Analysis by Karl Fischer Coulometry		AM1346 ¹	0.18%
Inorganic Content by Mi	croash Analysis	SP10-0135	< 0.2%
Mass Balance Purity Fac	tor		99.35%

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.

Spectral and Physical Data

GC/FID

FID	1 A, (RMA-013 P GC 6 2019-02-0	7 19-50-051B-0	02-37-RMA-013 FC	09101802.D)			
pA		N D					
7000-	('n					
6000-							
5000-							
4000 -							
3000							
2000		N00 -	040	Űτ	Ű		
1000-	7.63 7	000 N	900 1927	-0 04	ů Ú		
	, ", ", ", ", ", "			<u>, , , , , , , , , , , , , , , , , , , </u>	Ň		
Ó	5	10	15	20	25	30	35 min

Column:	DB-5ms 1.5 um	s, 30 m x 0.53 mm ID film thickness	,
Temp Prog	ram: 40°C to	9 80°C at 40°C/min	
	175°C t	to 300°C at 10°C/min	
Turio ato y To			
Injector le	mp: Cool-or	I-Column	
Detector Ie	emp: 325°C		
	FC0010	1002	
Sample Na	me: FC0910	1802	
Acquired:	Februar	ry 07, 2019	
Deals #	Dat Time	Awar 0/	
Peak #	Ret Time	Area %	
Peak #	Ret Time 8.77	Area %	
Peak #	Ret Time 8.77 9.16	Area % 0.01 0.04	
Peak #	Ret Time 8.77 9.16 9.60	Area % 0.01 0.04 99.53	
Peak # 1 2 3 4	Ret Time 8.77 9.16 9.60 10.14	Area % 0.01 0.04 99.53 0.05	
Peak # 1 2 3 4 5	Ret Time 8.77 9.16 9.60 10.14 10.72	Area % 0.01 0.04 99.53 0.05 0.01	
Peak # 1 2 3 4 5 6	Ret Time 8.77 9.16 9.60 10.14 10.72 11.30	Area % 0.01 0.04 99.53 0.05 0.01 0.16	
Peak # 1 2 3 4 5 6 7	Ret Time 8.77 9.16 9.60 10.14 10.72 11.30 12.77	Area % 0.01 0.04 99.53 0.05 0.01 0.16 0.01	
Peak # 1 2 3 4 5 6 7 8	Ret Time 8.77 9.16 9.60 10.14 10.72 11.30 12.77 14.59	Area % 0.01 0.04 99.53 0.05 0.01 0.16 0.01 0.11	
Peak # 1 2 3 4 5 6 7 8 9	Ret Time 8.77 9.16 9.60 10.14 10.72 11.30 12.77 14.59 14.71	Area % 0.01 0.04 99.53 0.05 0.01 0.16 0.01 0.11 0.04	

15.14

19.13

19.64

26.66

0.01

0.00

0.00

0.02

11

12

13

14

Spectral and Physical Data (cont.)

HPLC/UV



Column:	Ascenti	s Express P	henyl-He	exyl,
	2.7 µm	, 3.0 x 100	mm	
Mobile Phase	e: A: Acet	onitrile		
	B: 0.19	% Phosphori	ic acid in	Water
Gradient:	Time (r	nin) %A	% B	
	0.00) 5	95	-
	3.50) 40	60	
	5.50) 40	60	
	5.51	. 5	95	
Flow Rate:	0.6 mL	/min		
Wavelength:	210 nm	า		
_				
Sample Nam	e: FC0910	1802		
Acquired:	Januar	23, 2019		
-				
Peak #	Ret Time	Area %	D	
Peak # 1	Ret Time 0.69	Area % 0.02	0	
Peak # 1 2	Ret Time 0.69 2.05	Area % 0.02 0.03	<u>0</u>	
Peak # 1 2 3	Ret Time 0.69 2.05 2.12	Area % 0.02 0.03 0.18	<u>0</u>	
Peak # 1 2 3 4	Ret Time 0.69 2.05 2.12 2.31	Area % 0.02 0.03 0.18 0.01	<u>0</u>	
Peak # 1 2 3 4 5	Ret Time 0.69 2.05 2.12 2.31 2.35	Area % 0.02 0.03 0.18 0.01 0.06	<u>0</u>	
Peak # 1 2 3 4 5 6	Ret Time 0.69 2.05 2.12 2.31 2.35 2.44	Area % 0.02 0.03 0.18 0.01 0.06 99.45	<u>.</u>	
Peak # 1 2 3 4 5 6 7	Ret Time 0.69 2.05 2.12 2.31 2.35 2.44 2.66	Area % 0.02 0.03 0.18 0.01 0.06 99.45 0.05	0	
Peak # 1 2 3 4 5 6 7 8	Ret Time 0.69 2.05 2.12 2.31 2.35 2.44 2.66 2.73	Area % 0.02 0.03 0.18 0.01 0.06 99.45 0.05 0.01	0	
Peak # 1 2 3 4 5 6 7 8 9	Ret Time 0.69 2.05 2.12 2.31 2.35 2.44 2.66 2.73 2.93	Area % 0.02 0.03 0.18 0.01 0.06 99.45 0.05 0.01 0.01	0	
Peak # 1 2 3 4 5 6 7 8 9 10	Ret Time 0.69 2.05 2.12 2.31 2.35 2.44 2.66 2.73 2.93 2.96	Area % 0.02 0.03 0.18 0.01 0.06 99.45 0.05 0.01 0.01 0.01 0.08	0	
Peak # 1 2 3 4 5 6 7 8 9 10 11	Ret Time 0.69 2.05 2.12 2.31 2.35 2.44 2.66 2.73 2.93 2.96 3.05	Area % 0.02 0.03 0.18 0.01 0.06 99.45 0.05 0.01 0.01 0.01 0.08 0.01	0	
Peak # 1 2 3 4 5 6 7 8 9 10 11 12	Ret Time 0.69 2.05 2.12 2.31 2.35 2.44 2.66 2.73 2.93 2.96 3.05 3.38	Area % 0.02 0.03 0.18 0.01 0.06 99.45 0.05 0.01 0.01 0.08 0.01 0.00	0	
Peak # 1 2 3 4 5 6 7 8 9 10 11 12 13	Ret Time 0.69 2.05 2.12 2.31 2.35 2.44 2.66 2.73 2.93 2.96 3.05 3.38 4.67	Area % 0.02 0.03 0.18 0.01 0.06 99.45 0.05 0.01 0.01 0.01 0.08 0.01 0.00 0.00	0	

15

4.87

0.02

Residual Solvent Analysis by GC/FID Headspace



¹H NMR JEOL ECS 400 Instrument: Solvent: Chloroform-D Q01231905 PROTON-5.jdf Signature: File is not signed, printed by adaydy RMA-013_FC09101802 8.0 20 0.0 3.0 2.0 40 3.0 50 102 1.0 bundance **3**.0 9.0 6.0 4.0 8.0 10.0 7.0 5.0 2.0 1.0 12897 12718 11852 2.7263 2.6933 2.6935 2.5325 2. L1190 X : parts per Million : 1H

GC/MS



Stability

Short term stability studies have been performed in multiple storage conditions for a period of up to four weeks. Short term data is utilized 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 stability findings for a related product (A-016, (\pm) -Amphetamine-D₁₁) is listed below.

Storage Condition	Mean Kinetic Temperature (MKT)	Time Period/Result		
Freezer	-15°C			
Refrigerator	4°C	No decrease in purity was noted after		
Room Temperature	21°C	four weeks.		
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	March 10, 2020	Initial version.



Certified Reference Material - Certificate of Analysis

(±)-Amphetamine-D₅ (SC), Primary Measurement Standard

	(±)-1-Phenyl-1,2,3,3,3-pentadeutero-2-aminopropane	Cerilliant Quality
Product No.:	A-013-1ML	ISO 17034
Lot No.:	FE03232004	ISO/IEC 17025
Description of CRM:	(±)-Amphetamine-D ₅ (SC) in Methanol (Solution)	130/120 17023
Expiration Date:	April 2025 See Section "Stability Assessment".	ISO 13485
Storage:	Store unopened in freezer (-10 °C to -25 °C).	ISO 14001
Shipping:	Ambient. See Section "Stability Assessment". D H	ISO 9001
Chemical formula:	C ₉ H ₈ D ₅ N	
CAS No.:	136765-27-0	3
Regulatory:	USDEA Exempt Canadian TK # 61-993	

Analyte	Certified Concentration ± associated uncertainty U, u=k*u (k=2)
(±)-Amphetamine-D $_5$ (SC)	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 correctConcentration is corrected for chromatographic purity, residual water, residual
solvents, and residual inorganics. No adjustment required before use.use:Users should quantitatively transfer desired volume using established good
laboratory practices to spike into matrix or to dilute to the desired

Health and safety information:

Accreditation:

Danger. Please refer to the Safety Data Sheet for detailed information about the nature of any hazard and appropriate precautions to be taken.
 Cerilliant Corp. is accredited by the US accreditation authority ANAB as registered reference material producer AR-1353 in accordance with ISO 17034 and registered testing laboratory AT-1352 according to ISO/IEC 17025.

For MS Applications, we advise laboratories not to mix lots during a single

concentration. Each ampoule is intended for one-time use.



sequence.

Darron Ellsworth, Quality Assurance Manager

May 08, 2020

Issue Date

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 17034 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.



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 17034, 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 calculated 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 are analytically 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	Number of Points:	4
	thickness	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		
	Varified Concentration		

		Vermed Concentration (mg/mL)	7883D - Hullugelleity
Standard Solution	Lot Number	Actual Results	Actual Results
New Lot	FE03232004	0.989	0.9
Previous Lot	FE06061601	0.983	1.2

 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: Material Lot:	(±)-Amphetamine-D ₅ (SC) FC08191504	Chemical Form CAS Number: Molecular Weig	nula: C₀l 13 ght: 14	H ₈ D₅N 6765-27-0 0.24
	Material Characte	erization Summary		
Analytical Test		Method	Re	sults
Primary Chromatographi	c Purity by GC/FID Analysis	SP10-0101	99	.8%
Secondary Chromatogra	phic Purity by HPLC/UV Analysis	SP10-0102	99	9%
Identity by LC/MS Analysis		SP10-0107	Consistent with Structure	
			0.00%	D ₀ vs D ₅
Isotopic Purity and Distribution by LC/MS SIM Analysis		SP10-0107	0.00% D ₀	0.16% D ₃
			0.03% D ₁	4.63% D ₄
			0.60% D ₂	94.59% D ₅
Identity by ¹ H-NMR Analysis		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	1.59%	
Mass Balance Purity Factor			98	24%

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.

Spectral and Physical Data

GC/FID



Column:	DB-5 1.5 µ	5ms, 30 m x 0.53 m um film thickness	nm ID,
Temp Progr	am: 40°C	C to 80°C at 40°C/n	nin
	80°C	C to 175°C at 5°C/n	nin
	175°	°C to 300°C at 10°C	C/min hold 5 min
Injector Tei	mp: Cool	-on-Column	
Detector Te	mp: 325°	°C	
Sample Nar	ne: FCO8	3191504 Sember 24 2019	
Acquireu.	Sept		
Peak #	Ret Time	Area %	
1	6.71	0.01	
2	8.01	99.82	
3	9.00	0.16	
4	11.06	0.01	

Residual Solvent Analysis by GC/FID Headspace



ND - None Detected

Spectral and Physical Data (cont.)





Column:	Zorbax E	Bonus RP, 3	3.5 μm,	
	4.6 x 15	0 mm		
Mobile Phas	se: A: Aceto	nitrile		
	B: 20 ml	M Sodium p	perchlora	te with
	0.02% P	hosphoric a	acid	
Gradient:	Time (mi	n) % A	% B	
	0.0	10	90	
	2.0	10	90	
	12.0	50	50	
	17.0	50	50	
	17.1	10	90	
	23.0	10	90	
Flow Rate:	1.0 mL/r	nin		
Wavelength	1: 212 nm			
Sample Nar	ne: FC08191	504		
Acquired:	October	27, 2015		
Peak #	Ret Time	Area %		
1	5.67	0.01		
2	7.52	99.94		
3	8.10	0.01		
4	8.32	0.01		
5	8.46	0.01		
6	8.89	0.01		
7	9.99	0.01		
8	10.36	0.00		





Isotopic Purity by LC/MS SIM



Stability

Short term stability studies have been performed in multiple storage conditions for a period of up to four weeks. Short term data is utilized 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 stability findings for a related product (A-016, (\pm) -Amphetamine-D₁₁) is listed below.

Storage Condition	Mean Kinetic Temperature (MKT)	Time Period/Result
Freezer	-15°C	
Refrigerator	4°C	No decrease in purity was noted after
Room Temperature	21°C	four weeks.
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	May 08, 2020	Initial version.



Certified Reference Material - Certificate of Analysis

6-A0	cetylmorphine, Primary Measurement Standard	Cerilliant Quality
	7,8-Didehydro-4,5-epoxy-6-acetyl-17-methylmorphinan-3-ol	ISO 17034
Product No.:	A-009-1ML	ISO/IEC 17025
Lot No.:	FE01142009	ISO 13485
Description of CRM:	6-Acetylmorphine in Acetonitrile (Solution)	150 14001
Expiration Date:	January 2025 See Section "Stability Assessment".	130 14001
Storage:	Store unopened in freezer (-10 °C to -25 °C). HO_ \sim	ISO 9001
Shipping:	Ambient. See Section "Stability Assessment".	
Chemical formula:	C ₁₉ H ₂₁ NO ₄	\neg
CAS No.:	2784-73-8	-Ν CH
Regulatory:	USDEA Exempt Canadian TK # 61-990	0.13

Analyte		Certified Concentration \pm associated uncertainty U, $u=k*u$ (k=2)	
6-Acetylmorp	hine	$1.000 \pm 0.006 \text{ mg/mL}$	
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 μ L for quantitati	ive applications	
Instructions for handling and correct use:	Concentration is corrected for chromatographic purity, residual water, 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. 30 minute sonication required before use to ensure accurate		
Health and safety	Danger. Please re	fer to the Safety Data Sheet for detailed information about	
information:	the nature of any	nazaru 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 17034 and registered testing laboratory AT-1352 according to ISO/IEC 17025.		



Darron Ellsworth, Quality Assurance Manager

February 28, 2020

Issue Date

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 17034 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.



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 17034, 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 calculated 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 are analytically 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:	HPLC/UV	Calibration Curve:	Linear Regression
Column:	Ascentis Express C18, 2.7 µm, 3.0 x 100 mm	Number of Points:	4
Mobile Phase:	Acetonitrile:0.1% Phosphoric acid in Water (15:85)	Linearity (r) :	1.000
Flow Rate:	1.5 mL/min		
Wavelength:	230 nm		
	Varified Concentration	(mg/ml) = 0/1	PSD - Homogonoity

		vermed concentration (mg/mL)	%RSD - Homogeneity	
Standard Solution	Lot Number	Actual Results	Actual Results	
New Lot	FE01142009	0.997	0.6	
Previous Lot	FE07161901	1.003	0.2	

 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: Material Lot:	6-Acetylmorphine FC01111902	Chemical Form CAS Number: Molecular Weig	clight: C19H21NO4 2784-73-8 327.37
	Material Characte	erization Summary	
Analytical Test		Method	Results
Primary Chromatographi	ic Purity by HPLC/UV Analysis	SP10-0102	99.8% ¹
Secondary Chromatographic Purity by GC/FID Analysis		SP10-0101	99.3%
Identity by GC/MS Analysis		SP10-0105	Consistent with Structure
Identity by ¹ H-NMR Anal	ysis	USP <761>, SP10-0116	Consistent with Structure
Residual Solvent Analysi	s by GC/FID Headspace	AM1087 ²	1.63%
Residual Water Analysis by Karl Fischer Coulometry		AM1346 ²	Below Quantitation Limit
Inorganic Content by Mi	croash Analysis	SP10-0135	< 0.2%
Mass Balance Purity Fac	tor		98.21%

¹ 0.02% Morphine and 0.06% Heroin were detected by HPLC/UV analysis.

² 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.

Spectral and Physical Data

HPLC/UV



9

Peak 1 is identified as Morphine; Peak 9 is identified as Heroin.

4.99

0.06



Column:		DB- 1.0	DB-35ms, 30 m x 0.53 mm ID 1.0 um film thickness		
Temp Program:		ram: 40° 200	40°C to 200°C at 40°C/min 200°C to 280°C at 5°C /min		
		noid	1 18 min		
	Injector Te	mp: Coc	l-on-Column		
	Detector Te	emp: 325	°C		
Sample Name:		me: FCC	FC01111902		
	Acquired:	May	/ 10, 2019		
	Peak #	Ret Time	Area %		
	1	18.51	0.02		
	2	19.27	99.30		
	3	19.63	0.43		
	4	20.58	0.14		
	5	20.96	0.11		

Residual Solvent Analysis by GC/FID Headspace



¹H NMR



JEOL ECS 400

Instrument:

GC/MS



Stability

Short term stability studies have been performed in multiple storage conditions for a period of up to four weeks. Short term data is utilized 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 stability findings for this product is listed below.

Storage Condition	Mean Kinetic Temperature (MKT)	Time Period/Result		
Freezer	-15°C			
Refrigerator	4°C	No decrease in purity was noted after		
Room Temperature	21°C	four weeks.		
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	February 28, 2020	Initial version.



Certified Reference Material - Certificate of Analysis

6-Acetylmorphine-D₆, Primary Measurement Standard

 6α -trideuteroacetoxy-4, 5α -epoxy-17-trideuteromethylmorphin-7-en-3-ol

6α -trideuteroacetoxy-4,5 α -epoxy-17-trideuteromethylmorphin-7-en-3-ol			
Product No.:	A-027-1ML	ISO 17034	
Lot No.:	FE01202008	ISO/IEC 17025	
Description of CR	M: 6-Acetylmorphine-D ₆ in Acetonitrile (Solution)		
Expiration Date:	February 2025 See Section "Stability Assessment".	ISO 13485	
Storage:	Store unopened in freezer (-10 °C to -25 °C).	ISO 14001	
Shipping:	Ambient. See Section "Stability Assessment". HO	ISO 9001	
Chemical formula	: C ₁₉ H ₁₅ D ₆ NO ₄		
CAS No.:	152477-90-2	\ \	
Regulatory:	USDEA Exempt Canadian TK # 61-1000	[►] N _{CD3}	

Analyte		Certified Concentration ± associated uncertainty U, u=k*u (k=2)		
6-Acetylmorph	ine-D ₆	1.000 ± 0.006 mg/mL		
Metrological traceability:	Traceable to the S unbroken chain of page 2.	5I and higher order standards from NIST through an comparisons. See "Details on metrological traceability" on		
Measurement method:	The certified value characterized star page 2.	e is calculated from high precision weighing of thoroughly ting material. See "Details about certification process" on		
Intended use:	This Certified Refe calibration, and qu applications. Not	erence Material is suitable for the in vitro identification, uantification of the analyte(s) in analytical and R&D suitable for human or animal consumption.		
Minimum sample size:	1 μL for quantitati	ve applications		
Instructions for handling and correct use:	Concentration is corrected for chromatographic purity, residual water, 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.			
	45 minute sonic concentration.	ation required before use to ensure accurate		
Health and safety	For MS Application sequence. Danger. Please re	ns, we advise laboratories not to mix lots during a single fer to the Safety Data Sheet for detailed information about		
information:	the nature of any	nazard 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 17034 and registered testing laboratory AT-1352 according to ISO/IEC 17025.			



March 02, 2020

Darron Ellsworth, Quality Assurance Manager

Issue Date

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 17034 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.



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 17034, 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 calculated 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 are analytically 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:	HPLC/UV	Calibration Curve:	Linear Regression
Column:	Ascentis Express C18, 2.7 µm, 3.0 x 100 mm	Number of Points:	4
Mobile Phase:	Acetonitrile:0.1% Phosphoric acid in Water (10:90)	Linearity (r) :	1.000
Flow Rate:	1.5 mL/min		
Wavelength:	230 nm		
	Verified Concentration	n (mg/mL) %	RSD - Homogeneity

		vermed concentration (mg/me)	/itto = nonogeneity	
Standard Solution	Lot Number	Actual Results	Actual Results	
New Lot	FE01202008	0.998	0.7	
Previous Lot	FE02091605	0.986	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.

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: Material Lot:	6-Acetylmorphine-D ₆ FC05081702	Chemical Form CAS Number:	nula: C ₁₉ H 152	la: C ₁₉ H ₁₅ D ₆ NO ₄ 152477-90-2	
		Molecular Wei	ght: 333.41		
	Material Characte	erization Summary			
Analytical Test		Method	Results		
Primary Chromatographic	Purity by GC/FID Analysis	SP10-0101	99.7	'% ¹	
Secondary Chromatograp Analysis	hic Purity by HPLC/UV	SP10-0102	99.8	3% ²	
Identity by GC/MS Analys	sis	SP10-0105	Consistent w	ith Structure	
			0.07% D ₀ vs D ₆		
			0.06% D ₀	1.22% D ₄	
Isotopic Purity and Distribution by GC/MS SIM Analysis		SP10-0105	0.07% D ₁	12.27% D ₅	
			0.08% D ₂	86.13% D ₆	
			0.18% D ₃		
Identity by LC/MS Analys	is	SP10-0107	Consistent with Structure		
			0.00% D ₀ vs D ₆		
Icotopic Durity and Distri	hution by LC/MC CIM Applycia	CD10 0107	0.00% D_0 to D_2	6.07% D ₅	
	DUCION DY LC/MS SIM ANALYSIS	SP10-0107	0.01% D ₃	93.80% D ₆	
			0.11% D ₄		
Identity by ¹ H-NMR Analysis		USP <761>, SP10-0116	Consistent with Structure		
Residual Solvent Analysis by GC/FID Headspace		AM1087 ³	1.73%		
Residual Water Analysis I	Residual Water Analysis by Karl Fischer Coulometry		Below Quantitation Limit		
Inorganic Content by Mic	Inorganic Content by Microash Analysis		< 0.2%		
Mass Balance Purity Factor			97.97%		

 1 0.08% Morphine-D₃ and 0.21% Heroin-D₉ detected by GC/FID analysis.

² 0.02% Heroin-D₉ detected by HPLC/UV analysis.

³ 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.

Spectral and Physical Data

GC/FID



HPLC/UV

	DAD1 A, Sig=230,4 Ref=off (004-P1-C2-RMA-006 FC05081702.D)	Column:		Ascentis Ex	scentis Express C18, 2.7 µm			
mAU .	648			3.0 x 100 m	nm			
200	, j	Mobile Pha	se:	A: Acetoniti	rile			
300-				B: 0.1% Phosphoric acid in Water				
		Gradient:		Time (min)	% A	% B	_	
250 -				0.0	5	95	-	
				8.0	50	50		
200-				10.0	50	50		
				10.1	5	95		
150 -		Flow Rate:		0.7 mL/min				
		Wavelengt	h:	230 nm				
100-								
		Sample Name: FC0		FC0508170	2			
		Acquired:		July 02, 2018				
50-								
	-1985 -1955 -1955 -1957	Peak #	Ret T	'ime /	Area %			
0-		1	3.0)8	99.79			
	<u>2</u> 4 6 8 10 mir	2	3.3	39	0.03			
		3	3.5	52	0.03			
		4	4.5	56	0.02	Her	oin-D ₉	
		5	6.0)5	0.03			

6

7.19

0.10
Residual Solvent Analysis by GC/FID Headspace



¹H NMR



Cerilliant Corporation, 811 Paloma Drive, Suite A Round Rock, TX 78665, USA, Tel: 800-848-7837 / 512-238-9974

Certificate Page 7 of 11

LC/MS



Isotopic Purity by LC/MS SIM



Certificate Page 9 of 11

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GC/MS



Stability

Short term stability studies have been performed in multiple storage conditions for a period of up to four weeks. Short term data is utilized 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 stability findings for a related product (A-006, 6-Acetylmorphine-D₃) is listed below.

Storage Condition	Mean Kinetic Temperature (MKT)	Time Period/Result	
Freezer	-15°C		
Refrigerator	4°C	No decrease in purity was noted afte four weeks.	
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	March 02, 2020	Initial version.



Certified Reference Material - Certificate of Analysis

Alp	prazolam, Primary Measurement Standard	Cerilliant Quality
8-chlor	o-1-methyl-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine	ISO 17034
Product No.:	A-903-1ML	ISO/IEC 17025
Lot No.:	FE02042004	ISO 13485
Description of CRM:	Alprazolam in Methanol (Solution)	150 14001
Expiration Date:	March 2025 See Section "Stability Assessment".	130 14001
Storage:	Store unopened in freezer (-10 °C to -25 °C).	ISO 9001
Shipping:	Ambient. See Section "Stability Assessment".	
Chemical formula:	C ₁₇ H ₁₃ ClN ₄	
CAS No.:	28981-97-7 CI	
Regulatory:	USDEA Exempt Canadian TK # 61-1027	

Analyte		Certified Concentration \pm associated uncertainty U, u=k*u (k=2)	
Alprazolan	n	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 μ L for quantitative applications		
Instructions for handling and correct use: Health and safety	Concentration is corrected for chromatographic purity, residual water, 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.		
information:	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 17034 and registered testing laboratory AT-1352 according to ISO/IEC 17025.		



Darron Ellsworth, Quality Assurance Manager

April 01, 2020

Issue Date

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 17034 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.



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 17034, 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 calculated 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 are analytically 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:	HPLC/UV	Calibration Curve:	Linear Regression
Column:	Ascentis Express Phenyl-Hexl, 2.7 μm, 3.0 x 100 mm	Number of Points:	4
Mobile Phase:	Acetonitrile:0.1% Ammonium acetate in Water (50:50)	Linearity (r) :	0.999
Flow Rate:	1.0 mL/min		
Wavelength:	238 nm		
	Verified Concentrat	on (mg/mL) %	6RSD - Homogeneity

Standard Solution	Lot Number	Actual Results	Actual Results
New Lot	FE02042004	0.994	1.5
Previous Lot	FE07061604	1.011	0.9

• 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: Material Lot:	Alprazolam FC09191907	Chemical Form CAS Number: Molecular Weig	iula: C ₁₇ H ₁₃ ClN ₄ 28981-97-7 ght: 308.76
	Material Characte	erization Summary	
Analytical Test		Method	Results
Primary Chromatographi	ic Purity by HPLC/UV Analysis	20384348	99.9%
Secondary Chromatographic Purity by GC/FID Analysis		20384346	98.2%
Identity by LC/MS Analysis		20384217	Consistent with Structure
Identity by ¹ H-NMR Analysis		20384224	Consistent with Structure
Residual Solvent Analysis by GC/FID Headspace		20397799 ¹	None Detected
Residual Water Analysis by Karl Fischer Coulometry		20398075 ¹	Not Detected
Inorganic Content by Microash Analysis		20384350	< 0.2%
Mass Balance Purity Fact	tor		99.87%

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.

Spectral and Physical Data

HPLC/UV



Column:	Ascentis Express Phenyl Hexyl,			
	2.7 µm, 3.0	x 100 n	nm	
Mobile Phase:	A: Acetonit	rile		
	B: 0.1% An	nmonium	n acetate	in Water
Gradient:	Time (min)	% A	% B	
	0.0	25	75	
	8.0	70	30	
	10.0	70	30	
	10.1	25	75	
Flow Rate:	0.7 mL/min			
Wavelength:	238 nm			
Sample Name:	FC0919190	7		
Acquired:	January 31,	2020		
Peak # Ret	Time /	Area %		
1 2.	.81	0.04		
2 3.	.01	0.08		
3 3.	89	0.01		
4 3.	98	99.86		

0.00

GC/FID



Column:	DB-5m 1.5 μm	s, 30 m x 0.53 mm film thickness	ID,
Temp Prog	gram: 40°C to 200°C	40°C to 200°C at 40°C/min 200°C to 300°C at 5°C/min	
	hold 16	5 min	-
Injector T	emp: Cool-or	n-Column	
Detector T	emp: 325°C		
Converte No	FC0010	1007	
Sample Na	ame: FC0919	91907	
Acquired:	Januar	y 30, 2020	
Peak #	Pot Timo	Area %	
Peak #	Ret Time	Area %	
Peak #	Ret Time 16.07	Area %	
Peak # 1 2	Ret Time 16.07 20.46	Area % 0.04 1.56	
Peak #	Ret Time 16.07 20.46 21.07	Area % 0.04 1.56 0.05	
Peak # 1 2 3 4	Ret Time 16.07 20.46 21.07 21.75	Area % 0.04 1.56 0.05 0.05	
Peak # 1 2 3 4 5	Ret Time 16.07 20.46 21.07 21.75 22.66	Area % 0.04 1.56 0.05 0.05 98.18	
Peak # 1 2 3 4 5 6	Ret Time 16.07 20.46 21.07 21.75 22.66 23.81	Area % 0.04 1.56 0.05 0.05 98.18 0.11	
Peak # 1 2 3 4 5 6 7	Ret Time 16.07 20.46 21.07 21.75 22.66 23.81 24.94	Area % 0.04 1.56 0.05 0.05 98.18 0.11 0.01	

4.56

5

Residual Solvent Analysis by GC/FID Headspace



¹H NMR



Instrument:

JEOL ECS 400

Cerilliant Corporation, 811 Paloma Drive, Suite A Round Rock, TX 78665, USA, Tel: 800-848-7837 / 512-238-9974

LC/MS Column: Ascentis Express C18, 2.7 µm, 0.4 mL/min Flow Rate: 3.0 x 50 mm 100-1200 amu Scan Range: Mobile Phase: A: 0.1% Formic acid in Water Ionization: Electrospray, Positive Ion B: Acetonitrile Waters XEVO G2 QTOF Instrument: Gradient: Time (min) % A % B Acquired: January 31, 2020 0.0 80 20 0.5 80 20 4.0 20 80 5.8 80 20 6.0 80 20 8.0 80 20 RMA-008 FC09191907 Cone Voltage: 20.0000000 **Alprazolam** W01312031 696 (2.621) Cm (693:702) 1: TOF MS ES+ 309.0907 100-Theoretical [M + H]+: 309.0907 Found [M + H]⁺: 309.0907 % 311.0881 205.0768 312.0908 639.1566 204.0755 0------ m/z

600

700

800

900

1000

1100

500

400

200

100

300

6.70e6

Stability

Short term stability studies have been performed in multiple storage conditions for a period of up to four weeks. Short term data is utilized 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 stability findings for this product is listed below.

Storage Condition	Mean Kinetic Temperature (MKT)	Time Period/Result	
Freezer	-15°C		
Refrigerator	4°C	No decrease in purity was noted aften four weeks.	
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	April 01, 2020	Initial version.



Certified Reference Material - Certificate of Analysis

Alpra	zolam-D ₅ , Prim	ary Measurement Sta	indard	Cerilliant Quality
8-chloro-1	-methyl-6-phenyl-4H-[1,2,4]triazolo[4,3-α][1,4]benzod	iazepine-D ₅	ISO 17034
Product No.:	A-910-1ML			100 /150 17005
Lot No.:	FE02042006			ISO/IEC 17025
Description of CRM:	Alprazolam-D ₅ in M	lethanol (Solution)		ISO 13485
Expiration Date:	February 2025	See Section "Stability Asses	sment".	ISO 14001
Storage:	Store unopened in	freezer (-10 °C to -25 °C).		ISO 9001
Shipping:	Ambient. See	Section "Stability Assessment".	Cĺ	
Chemical formula:	$C_{17}H_8CID_5N_4$			
CAS No.:	125229-61-0			∠ _сн₃
Regulatory:	USDEA Exempt C	anadian TK # 61-1032		N N

Analyte		Certified Concentration \pm associated uncertainty U, $u=k*u$ (k=2)		
Alprazolam-	•D ₅	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 characterized star page 2.	e is calculated from high precision weighing of thoroughly ting material. See "Details about certification process" on		
Intended use:	This Certified Refe calibration, and q applications. Not	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 μ L for quantitat	1 μL for quantitative applications		
Instructions for handling and correct use:	Concentration is of solvents, and resi Users should quar laboratory practic concentration. Ea For MS Application sequence.	corrected for chromatographic purity, residual water, residual dual inorganics. No adjustment required before use. ntitatively transfer desired volume using established good es to spike into matrix or to dilute to the desired ch ampoule is intended for one-time use. ns, we advise laboratories not to mix lots during a single		
Health and safety information:	Danger. Please re the nature of any	fer to the Safety Data Sheet for detailed information about hazard and appropriate precautions to be taken.		
Accreditation:	Cerilliant Corp. is registered referen and registered tes	accredited by the US accreditation authority ANAB as ice material producer AR-1353 in accordance with ISO 17034 sting laboratory AT-1352 according to ISO/IEC 17025.		



March 10, 2020

Darron Ellsworth, Quality Assurance Manager

Issue Date

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 17034 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.



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 17034, 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 calculated 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 are analytically 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 C	Curve	
Analysis Method:	HPLC/UV		Calibration C	Curve:	Linear Regression
Column:	Ascentis Express C1	Ascentis Express C18, 2.7 µm, 3.0 x 50 mm		Number of Points: 4	
Mobile Phase:	Acetonitrile:Water ((50:50)	Linearity (r)	:	0.999
Flow Rate:	1.2 mL/min				
Wavelength:	238 nm				
		Verified Concentration	n (mg/mL)	%F	RSD - Homogeneity

Standard	Lot Number	Actual Posults	Actual Poculta
Solution	Lot Number	Actual Results	Actual Results
New Lot	FE02042006	0.991	1.2
Previous Lot	FE08211802	0.994	0.8

• 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:Alprazolam-D5Chemical FormMaterial Lot:FC05011901CAS Number:Molecular Weig		ula: $C_{17}H_8CID_5N_4$ 125229-61-0 ght: 313.80					
	Material Characterization Summary						
Analytical Test		Method	Res	sults			
Primary Chromatographi	c Purity by HPLC/UV Analysis	SP10-0102	99	.5%			
Secondary Chromatogra	phic Purity by GC/FID Analysis	SP10-0101	98	.3%			
Identity by LC/MS Analy	sis	SP10-0107	Consistent v	vith Structure			
			0.02%	D ₀ vs D ₅			
Instania Durity and Distri	buties by LC/MC SIM Applying	SP10-0107	0.02% D ₀	0.02% D ₃			
150topic Purity and Distri	IDUTION DY LC/MIS SIM ANALYSIS		0.01% D ₁	1.83% D ₄			
			0.01% D ₂	98.12% D ₅			
Identity by ¹ H-NMR Anal	ysis	USP <761>, SP10-0116	Consistent v	with Structure			
Residual Solvent Analysi	s by GC/FID Headspace	AM1087 ¹	0.35%				
Residual Water Analysis	by Karl Fischer Coulometry	AM1346 ¹	Not Detected				
Inorganic Content by Mic	croash Analysis	SP10-0135	< 0.2%				
Mass Balance Purity Fact	tor		99.	15%			

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.

Spectral and Physical Data

HPLC/UV



10

11

GC/FID



	Column: Temp Prog Injector To Detector T	DB-5m 1.5 µm 40°C to 200°C hold 16 emp: Cool-or femp: 325°C	DB-5ms, 30 m x 0.53 mm ID 1.5 µm film thickness 40°C to 200°C at 40°C/min 200°C to 300°C at 5°C/min hold 16 min Cool-on-Column 325°C	
	Sample Na Acquired:	me: FC0501 August	1901 29, 2019	
	Peak #	Ret Time	Area %	
I	1	20.20	1.43	
I	2	20.80	0.07	
I	3	21.51	0.02	
	4	22.41	98.32	
'n	5	22.59	0.02	
	6	22.72	0.05	
	7	23.69	0.10	

3.82

3.88

0.01

0.03

Residual Solvent Analysis by GC/FID Headspace



¹H NMR

Instrument:	JEOL ECS 400
Solvent:	Chloroform-D



LC/MS

Column:	Ascentis Exp 3.0 x 50 mm	ress C1	.8, 2.7 μm	1	Flow Rate: Scan Range:	0.4 mL/min 100-1200 amu
Mobile Phase:	A: 0.1% For	mic acio	d in Water		Ionization:	Electrospray, Positive Ion
	B: Acetonitri	le			Instrument:	Waters XEVO G2 QTOF
Gradient:	Time (min)	% A	% B		Acquired:	August 15, 2019
	0.0	90	10			
	0.5	90	10			
	4.0	50	50			
	5.8	50	50			
	6.0	90	10			
	8.0	90	10			
				Alprazolam-D5		Cone Voltage: 20.0000000



Isotopic Purity by LC/MS SIM



Stability

Short term stability studies have been performed in multiple storage conditions for a period of up to four weeks. Short term data is utilized 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 stability findings for a related product (A-903, Alprazolam) is listed below.

Storage Condition	Mean Kinetic Temperature (MKT)	Time Period/Result		
Freezer	-15°C			
Refrigerator	4°C	No decrease in purity was noted after		
Room Temperature	21°C	four weeks.		
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	March 10, 2020	Initial version.



Certified Reference Material - Certificate of Analysis

alpha-Hydroxyalprazolam, Primary Measurement Standard

 $(8-chloro-6-phenyl-4H-[1,2,4]triazolo[4,3-\alpha][1,4]benzodiazepin-1-yl)methanol$

Product No.:	A-907-1ML	Cermiani Quany
Lot No.:	FN02042005	ISO 17034
Description of CRM:	alpha-Hydroxyalprazolam in Methanol (Solution)	ISO/IEC 17025
Expiration Date:	February 2025 See Section "Stability Assessment".	ISO 13485
Storage:	Store unopened in freezer (-10 °C to -25 °C).	ISO 14001
Shipping:	Ambient. See Section "Stability Assessment".	ISO 9001
Chemical formula:	C ₁₇ H ₁₃ ClN ₄ O	
CAS No.:	37115-43-8	
Regulatory:	Canadian TK # 61-1030	

Analyte		Certified Concentration \pm associated uncertainty U, u=k*u (k=2)
alpha-Hydroxyalp	razolam	1.000 ± 0.006 mg/mL
Metrological traceability:	Traceable to the S unbroken chain of page 2.	SI and higher order standards from NIST through an for the standards from NIST through an for the standards from the standards for the sta
Measurement method:	The certified value characterized star page 2.	e is calculated from high precision weighing of thoroughly ting material. See "Details about certification process" on
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 μ L for quantitat	ve applications
Instructions for handling and correct use: Health and safety information:	Concentration is of solvents, and resi Users should quar laboratory practic concentration. Ea Danger. Please res the nature of any	corrected for chromatographic purity, residual water, residual dual inorganics. No adjustment required before use. ntitatively transfer desired volume using established good es to spike into matrix or to dilute to the desired ch ampoule is intended for one-time use. fer to the Safety Data Sheet for detailed information about hazard and appropriate precautions to be taken.
Accreditation:	Cerilliant Corp. is registered referer and registered tes	accredited by the US accreditation authority ANAB as ice material producer AR-1353 in accordance with ISO 17034 sting laboratory AT-1352 according to ISO/IEC 17025.



Darron Ellsworth, Quality Assurance Manager

March 09, 2020

Issue Date

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 17034 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.



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 17034, 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 calculated 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 are analytically 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:	HPLC/UV		Calibration	Curve:	Linear Regression
Column:	Ascentis Express C18, 2.7 µm, 3.0 x 100 mm		Number of Points: 4		4
Mobile Phase:	Acetonitrile:0.1% Ammonium acetate in Water (40:60)		Linearity (r):	1.000
Flow Rate:	1.2 mL/min				
Wavelength:	238 nm				
		Verified Concentratio	n (mg/mL)	%F	RSD - Homogeneity

Standard Solution	Lot Number	Actual Results	Actual Results
New Lot	FN02042005	0.993	0.5
Previous Lot	FN07051601	0.996	0.7

• 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: Material Lot:	alpha-Hydroxyalprazolam FN03311612	Chemical Form CAS Number: Molecular Weig	ula: C ₁₇ H ₁₃ ClN ₄ O 37115-43-8 ght: 324.76
	Material Characte	erization Summary	
Analytical Test		Method	Results
Primary Chromatographic Purity by HPLC/UV Analysis		20384348	99.9% ¹
Secondary Chromatographic Purity by LC/MS Analysis		20384217	98.7%
Identity by LC/MS Analy	/sis	20384217	Consistent with Structure
Identity by ¹ H-NMR Analysis		20384224	Consistent with Structure
Residual Solvent Analysis by GC/FID Headspace		20397799 ²	None Detected
Residual Water Analysis by Karl Fischer Coulometry		20398075 ²	Below Quantitation Limit
Inorganic Content by Microash Analysis		20384350	< 0.2%
Mass Balance Purity Factor			99.91%

¹ 0.02% Estazolam detected by HPLC/UV analysis; no Alprazolam detected.

² 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.

Spectral and Physical Data

HPLC/UV



Peak 4 has been identified as Estazolam

Residual Solvent Analysis by GC/FID Headspace

FID1 & Freet Simal (F-0116-05-10-14-36-97-RVIH-014 EN03311612 D)	Column:		DB-ALC1 30 m	x 0.53 mm,
ρΑ 100-			3 µm film thick	ness
	Temp Pr	ogram:	40°C hold 12 m	hin to 220°C at
		_	40°C/min hold	5.5 min
80 -	Carrier C	Gas:	Helium	
	Flow Rat	te:	2.0 mL/min	
- -	Detector	· Heater Temp:	250°C	
-	Injector		Headspace San	npler
	HS Oven	Temp:	60°C	
40-	Vial Equ	ilibration:	10 minutes	
	Sample	Name:	FN03311612	
	Acquired	1:	May 10, 2016	
0-	Peak	Compound	Area	Weight %
	1	NMP	NA	NA
	Total			ND
			ND - N	one Detected



LC/MS

Column:	Ascentis Exp	Ascentis Express C18, 2.7 µm,		Flow Rate:	0.4 mL/min
	3.0 x 50 mm	ı		Scan Range:	100-1200 amu
Mobile Phase:	A: 0.1% For	A: 0.1% Formic acid in Water		Ionization:	Electrospray, Positive Ion
	B: Acetonitri	le		Instrument:	Waters XEVO G2 QTOF
Gradient:	Time (min)	% A	% B	Acquired:	October 21, 2019
	0.0	90	10		
	0.5	90	10		
	4.0	50	50		
	5.8	50	50		
	6.0	90	10		
	8.0	90	10		





Stability

Short term stability studies have been performed in multiple storage conditions for a period of up to four weeks. Short term data is utilized 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 stability findings for a related product (A-908, alpha-Hydroxyalprazolam- D_5) is listed below.

Storage Condition	Mean Kinetic Temperature (MKT)	Time Period/Result	
Freezer	-15°C		
Refrigerator	4°C	No decrease in purity was noted after	
Room Temperature	21°C	four weeks.	
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	March 09, 2020	Initial version.



Certified Reference Material - Certificate of Analysis

alpha-Hydroxyalprazolam-D₅, Primary Measurement Standard

(8-chloro-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine-1-yl)Methanol-D 5

Product No.:	A-908-1ML	Cerninam Quality
Lot No.:	FN02202003	ISO 17034
Description of CRM:	alpha-Hydroxyalprazolam-D $_5$ in Methanol (Solution)	ISO/IEC 17025
Expiration Date:	February 2025 See Section "Stability Assessment".	ISO 13485
Storage:	Store unopened in freezer (-10 °C to -25 °C).	ISO 14001
Shipping:	Ambient. See Section "Stability Assessment".	150 9001
Chemical formula:	C ₁₇ H ₈ CID ₅ N ₄ O	150 7001
CAS No.:	136765-24-7	
Regulatory:	Canadian TK # 61-1031	

Analyte		Certified Concentration \pm associated uncertainty U, u=k*u (k=2)
alpha-Hydroxyalpra	azolam-D ₅	1.000 ± 0.006 mg/mL
Metrological traceability:	Traceable to the S unbroken chain of page 2.	5I and higher order standards from NIST through an comparisons. See "Details on metrological traceability" on
Measurement method:	The certified value characterized star page 2.	e is calculated from high precision weighing of thoroughly ting material. See "Details about certification process" on
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 μ L for quantitati	ve applications
Instructions for handling and correct use:	Concentration is corrected for chromatographic purity, residual water, 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. For MS Applications, we advise laboratories not to mix lots during a single sequence	
Health and safety information:	Danger. Please re the nature of any	fer to the Safety Data Sheet for detailed information about hazard and appropriate precautions to be taken.
Accreditation:	Cerilliant Corp. is registered referen and registered tes	accredited by the US accreditation authority ANAB as ice material producer AR-1353 in accordance with ISO 17034 sting laboratory AT-1352 according to ISO/IEC 17025.



April 20, 2020

Darron Ellsworth, Quality Assurance Manager

Issue Date

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 17034 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.



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 17034, 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 calculated 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 are analytically 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:	HPLC/UV		Calibration	Curve:	Linear Regression
Column:	Ascentis Express C18, 2.7 µm, 3.0 x 50 mm		Number of I	Points:	4
Mobile Phase:	Acetonitrile:Water (50:50)		Linearity (r)):	0.999
Flow Rate:	1.5 mL/min				
Wavelength:	238 nm				
		Verified Concentration	n (mg/mL)	%F	SD - Homogeneity

Standard Solution	Lot Number	Actual Results	Actual Results
New Lot	FN02202003	1.016	0.5
Previous Lot	FN07311803	1.005	1.5

• 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: Material Lot:	alpha-Hydroxyalprazolam-D FN10041908	Chemical Form CAS Number: Molecular Wei	ula: C ₁₇ H ₈ ClD ₅ N₄O 136765-24-7 Jht: 329.80		
	Material Characte	erization Summary			
Analytical Test		Method	Res	ults	
Primary Chromatograph	ic Purity by HPLC/UV Analysis	20384348	99.	5%	
Secondary Chromatogra	phic Purity by LC/MS Analysis	20384217	97.	4%	
Identity by LC/MS Analy	rsis	20384217	Consistent with Structure		
			0.01%	D ₀ vs D ₅	
Isotopic Purity and Distr	ribution by LC/MS SIM Analysis	20384217	0.01% D_0 to D_2	1.85% D ₄	
			0.03% D ₃	98.09% D ₅	
Identity by ¹ H-NMR Ana	lysis	20384224	Consistent w	ith Structure	
Residual Solvent Analys	is by GC/FID Headspace	20397799	0.07%		
Residual Water Analysis	by Karl Fischer Coulometry	20398075	Not Detected		
Inorganic Content by Mi	croash Analysis	20384350	< 0.2%		
Mass Balance Purity Fac	tor		99.4	17%	

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.

Spectral and Physical Data

HPLC/UV



Column:	Ascentis	Ascentis Express C18, 2.7 µm,				
	3.0 x 50	3.0 x 50 mm				
Mobile Phas	A: Aceto	onitrile				
.	B: wate	er	04 F			
Gradient:	Time (m	<u>iin) % A</u>	<u>% B</u>			
	0.0	20	80			
	4.0	/0	30			
	5.0	70	30			
	5.1	20	80			
Flow Rate:	0.8 mL/	min				
Wavelength	238 nm					
Sample Nan	ne: FN1004	1908				
		~~ ~~~~				
Acquired:	January	23, 2020				
Acquired: Peak #	January Ret Time	23, 2020 Area %	D			
Acquired: Peak #	January Ret Time 1.94	23, 2020 Area % 0.02	0			
Acquired: Peak #	January Ret Time 1.94 2.02	23, 2020 Area % 0.02 0.01	0			
Acquired: Peak # 1 2 3	January Ret Time 1.94 2.02 2.15	23, 2020 Area % 0.02 0.01 0.01	<u>D</u>			
Acquired: Peak # 1 2 3 4	January Ret Time 1.94 2.02 2.15 2.24	23, 2020 Area % 0.02 0.01 0.01 0.01	<u>D</u>			
Acquired: Peak # 1 2 3 4 5	January Ret Time 1.94 2.02 2.15 2.24 2.40	23, 2020 Area % 0.02 0.01 0.01 0.01 99.54	0			
Acquired: Peak # 1 2 3 4 5 6	January Ret Time 1.94 2.02 2.15 2.24 2.40 2.51	23, 2020 Area % 0.02 0.01 0.01 99.54 0.35	0			
Acquired: Peak # 1 2 3 4 5 6 7	January Ret Time 1.94 2.02 2.15 2.24 2.40 2.51 2.83	23, 2020 Area % 0.02 0.01 0.01 99.54 0.35 0.00	<u>.</u>			
Acquired: Peak # 1 2 3 4 5 6 7 8	January Ret Time 1.94 2.02 2.15 2.24 2.40 2.51 2.83 2.89	23, 2020 Area % 0.02 0.01 0.01 0.01 99.54 0.35 0.00 0.00	<u>.</u>			
Acquired: Peak # 1 2 3 4 5 6 7 8 9	January Ret Time 1.94 2.02 2.15 2.24 2.40 2.51 2.83 2.89 3.15	23, 2020 Area % 0.02 0.01 0.01 99.54 0.35 0.00 0.00 0.00	0			
Acquired: Peak # 1 2 3 4 5 6 7 8 9 10	January Ret Time 1.94 2.02 2.15 2.24 2.40 2.51 2.83 2.89 3.15 3.19	23, 2020 Area % 0.02 0.01 0.01 99.54 0.35 0.00 0.00 0.00 0.00 0.00	0			
Acquired: Peak # 1 2 3 4 5 6 7 8 9 10 11	January Ret Time 1.94 2.02 2.15 2.24 2.40 2.51 2.83 2.89 3.15 3.19 3.25	23, 2020 Area % 0.02 0.01 0.01 99.54 0.35 0.00 0.00 0.00 0.00 0.00 0.00	0			

3.67

0.03

13

Residual Solvent Analysis by GC/FID Headspace



¹H NMR



LC/MS

Column:	Ascentis Express C18, 2.7 µm, 3.0 x 50 mm A: 0.1% Formic acid in Water			Flow Rate:	0.4 mL/min 100-1200 amu
Mobile Phase:				Scan Range:	
				Ionization:	Electrospray, Positive Ion
	B: Acetonitri	le		Instrument:	Waters XEVO G2 QTOF
Gradient:	Time (min)	% A	% B	Acquired:	January 23, 2020
	0.0	90	10		
	0.5	90	10		
	4.0	50	50		
	5.8	50	50		
	6.0	90	10		
	8.0	90	10		
RMH-015 FN1004190	8		alpha-Hydroxyalprazolam-D5	Co	ne Voltage: 20.00000000
W01232022 Sm (Mn, 1x	6)				1: TOF MS ES+
	•				TIC





Isotopic Purity by LC/MS SIM



Stability

Short term stability studies have been performed in multiple storage conditions for a period of up to four weeks. Short term data is utilized 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 stability findings for this product is listed below.

Storage Condition	Mean Kinetic Temperature (MKT)	Time Period/Result		
Freezer	-15°C			
Refrigerator	4°C	No decrease in purity was noted after		
Room Temperature	21°C	four weeks.		
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	April 20, 2020	Initial version.



Certified Reference Material - Certificate of Analysis

Cocaine, Primary Measurement Standard				
3-(Benzoyloxy)-8-methyl-8-azabicyclo[3,2,1]octane-2-carboxylic acid methyl ester				
Product No.:	C-008-1ML		ISO/IEC 17025	
Lot No.:	FE01202010		ISO 13485	
Description of CRM:	Cocaine in Acetor	nitrile (Solution)	ISO 14001	
Expiration Date:	February 2025	See Section "Stability Assessment".	130 14001	
Storage:	Store unopened i	in freezer (-10 °C to -25 °C).	ISO 9001	
Shipping:	Ambient. Se	ee Section "Stability Assessment".	CH ₂	
Chemical formula:	$C_{17}H_{21}NO_4$	~~~~		
CAS No.:	50-36-2		0	
Regulatory:	USDEA Exempt	Canadian TK # 61-1079		

Analyte		Certified Concentration \pm associated uncertainty U, u=k*u (k=2)		
Cocaine		1.000 ± 0.006 mg/mL		
Metrological traceability: Traceable to the subroken chain o page 2.		SI and higher order standards from NIST through an f comparisons. See "Details on metrological traceability" on		
Measurement method:	The certified value characterized star page 2.	e is calculated from high precision weighing of thoroughly ting material. See "Details about certification process" on		
Intended use: This Certified Ref calibration, and q applications. Not		erence Material is suitable for the in vitro identification, quantification of the analyte(s) in analytical and R&D suitable for human or animal consumption.		
Minimum sample size:	1 μ L for quantitat	ive applications		
Instructions for handling and correct use: Health and safety information:	Concentration is of solvents, and residusers should quar laboratory practico concentration. Ea Danger. Please residue the nature of any	corrected for chromatographic purity, residual water, residual dual inorganics. No adjustment required before use. htitatively transfer desired volume using established good es to spike into matrix or to dilute to the desired ch ampoule is intended for one-time use. fer to the Safety Data Sheet for detailed information about hazard and appropriate precautions to be taken.		
Accreditation:	Cerilliant Corp. is registered referer and registered tes	accredited by the US accreditation authority ANAB as a loce material producer AR-1353 in accordance with ISO 17034 sting laboratory AT-1352 according to ISO/IEC 17025.		



Darron Ellsworth, Quality Assurance Manager

March 18, 2020

Issue Date

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 17034 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.



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 17034, 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 calculated 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 are analytically 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	Calibration Curve				
Analysis Method:	HPLC/UV		Calibration	Curve:	Linear Regression
Column: Mobile Phase:	Ascentis Express C1 Acetonitrile:0.1% P (25:75)	Number of Points:4Linearity (r):1.000			
Flow Rate:	1.5 mL/min				
Wavelength:	235 nm				
		Verified Concentration	(mg/mL)	%R	RSD - Homogeneity
Standard					

Standard Solution	Lot Number	Actual Results	Actual Results
New Lot	FE01202010	1.001	0.4
Previous Lot	FE09091901	0.997	0.7

• 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: Material Lot:	Cocaine FE10301701	Chemical Form CAS Number: Molecular Weig	ula: C ₁₇ H ₂₁ NO ₄ 50-36-2 ght: 303.35
	Material Characte	erization Summary	
Analytical Test		Method	Results
Primary Chromatograph	ic Purity by HPLC/UV Analysis	SP10-0102	> 99.9% 1
Secondary Chromatographic Purity by GC/FID Analysis		SP10-0101	> 99.9%
Identity by GC/MS Analy	/sis	SP10-0105	Consistent with Structure
Identity by ¹ H-NMR Analysis		USP <761>, SP10-0116	Consistent with Structure
Residual Solvent Analysis by GC/FID Headspace		AM1087 ²	0.66%
Residual Water Analysis by Karl Fischer Coulometry		AM1346 ²	Below Quantitation Limit
Inorganic Content by Microash Analysis		SP10-0135	< 0.2%
Mass Balance Purity Fac	tor		99.33%

¹ 0.01% Cocaethylene detected by HPLC/UV analysis.

² 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.

Spectral and Physical Data

HPLC/UV



Peak 3 has been identified as Cocaethylene

0.01



GC/FID

Residual Solvent Analysis by GC/FID Headspace





GC/MS



Cerilliant Corporation, 811 Paloma Drive, Suite A Round Rock, TX 78665, USA, Tel: 800-848-7837 / 512-238-9974

Stability

Short term stability studies have been performed in multiple storage conditions for a period of up to four weeks. Short term data is utilized 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 stability findings for a related product (C-004, Cocaine-D₃) is listed below.

Storage Condition	Mean Kinetic Temperature (MKT)	Time Period/Result	
Freezer	-15°C		
Refrigerator	4°C	No decrease in purity was noted after	
Room Temperature	21°C	four weeks.	
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	March 18, 2020	Initial version.



Certified Reference Material - Certificate of Analysis

Cocaine-D ₃ , Primary Measurement Standard			
3-Benzoyloxy-8(tride	teromethyl)-8-azabicyclo[3.2.1]octane-2	carboxylic acid methyl ester?	ISO 17034
Product No.:	C-014-1ML		ISO/IEC 17025
Lot No.:	FE03022002		ISO 13485
Description of CRM:	Cocaine- D_3 in Acetonitrile (Solution)		ISO 14001
Expiration Date:	March 2025 See Section "	Stability Assessment".	ISO 9001
Storage:	Store unopened in freezer (-10 °C to	-25 °C).	
Shipping:	Ambient. See Section "Stability	Assessment". N COO	CH₃
Chemical formula:	C ₁₇ H ₁₈ D ₃ NO ₄	Ххан так	
CAS No.:	138704-14-0		
Regulatory:	USDEA Exempt Canadian TK # 61-1	082 H	-0-C-()

Analyte	Certified Concentration ± associated uncertainty U, u=k*u (k=2)
Cocaine-D ₃	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	Concentration is corrected for chromatographic purity, residual water, residual solvents, and residual inorganics. No adjustment required before use.
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.
	For MS Applications, we advise laboratories not to mix lots during a single sequence.
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 17034 and registered testing laboratory AT-1352 according to ISO/IEC 17025.



Darron Ellsworth, Quality Assurance Manager

April 20, 2020

Issue Date

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 17034 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.



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 17034, 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 calculated 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 are analytically 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:	HPLC/UV		Calibration Curve: Linear Regr		Linear Regression
Column:	Ascentis Express C18, 2.7 µm, 3.0 x 100 mm		Number of Points: 4		4
Mobile Phase:	Acetonitrile: 0.1% Phosphoric acid in Water (25:75)		Linearity (r) : 1.000		1.000
Flow Rate:	1.5 mL/min				
Wavelength:	235 nm				
		Verified Concentration	(mg/mL)	%R	SD - Homogeneity
Standard					

Standard Solution	Lot Number	Actual Results	Actual Results
New Lot	FE03022002	1.004	0.3
Previous Lot	FE07131601	1.007	0.2

 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: Material Lot:	Cocaine-D₃ FC12161903	Chemical Form CAS Number: Molecular Weig	nula: C ₁ 13 ght: 30	,H ₁₈ D ₃ NO₄ 8704-14-0 6.37
	Material Charact	erization Summary		
Analytical Test		Method	Re	sults
Primary Chromatographi	ic Purity by HPLC/UV Analysis	20384348	99	6% ¹
Secondary Chromatogra	phic Purity by GC/FID Analysis	20384346	99	9.6%
Identity by LC/MS Analysis		20384217	Consistent	with Structure
			0.02%	D ₀ vs D ₃
Isotopic Purity and Distr	ibution by LC/MS SIM Analysis	20384217	0.02% D ₀	0.34% D ₂
			0.01% D ₁	99.64% D ₃
Identity by ¹ H-NMR Analysis		20384224	Consistent	with Structure
Residual Solvent Analysis by GC/FID Headspace		20397799 ²	0.64%	
Residual Water Analysis by Karl Fischer Coulometry		20398075 ²	Not Detected	
Inorganic Content by Microash Analysis		20384350	<	0.2%
Mass Balance Purity Factor			98	.98%

¹ 0.19% Cocaethylene and < 0.01% Benzoyecgonine detected by HPLC/UV analysis.

² 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.

Spectral and Physical Data

HPLC/UV



Column:	Ascent	is Express	C18, 2.7 µr	n,
	3.0 x 1	100 mm		
Mobile Phase	e: A: Ace	tonitrile		
	B: 0.1	% Phospho	ric acid in \	Nate
Gradient:	Time (min) % A	% B	
	0.0) 10	90	
	1.0) 10	90	
	7.0) 60	40	
	9.0) 60	40	
	9.1	10	90	
Flow Rate:	0.8 ml	/min		
Wavelength	: 235 nr	n		
Sample Nam	e: FC121	61903		
Acquired	Echrug	ny 20 202	0	
Acquireu.	replua	ii y 20, 202	0	
Acquireu.	rebiua	iry 20, 202	0	
Peak #	Ret Time	Area •	%	
Peak #	Ret Time	Area ° 0.00	<u>% </u>	
Peak #	Ret Time 0.48 1.77	Area 0.00 0.04	%	
Peak # 1 2 3	Ret Time 0.48 1.77 3.24	Area 0.00 0.04 0.00	%	
Peak # 1 2 3 4	Ret Time 0.48 1.77 3.24 3.89	Area 0.00 0.04 0.00 99.56	<u>%</u>	
Peak # 1 2 3 4 5	Ret Time 0.48 1.77 3.24 3.89 4.13	Area 0.00 0.04 0.00 99.56 0.10	%	
Peak # 1 2 3 4 5 6	Ret Time 0.48 1.77 3.24 3.89 4.13 4.22	Area 0.00 0.04 0.00 99.56 0.10 0.05	%	
Peak # 1 2 3 4 5 6 7	Ret Time 0.48 1.77 3.24 3.89 4.13 4.22 4.37	Area 0.00 0.04 0.00 99.56 0.10 0.05 0.00	%	
Peak # 1 2 3 4 5 6 7 8	Ret Time 0.48 1.77 3.24 3.89 4.13 4.22 4.37 4.41	Area 0.00 0.04 0.00 99.56 0.10 0.05 0.00 0.00	%	
Peak # 1 2 3 4 5 6 7 8 9	Ret Time 0.48 1.77 3.24 3.89 4.13 4.22 4.37 4.41 4.47	Area 0.00 0.04 0.00 99.56 0.10 0.05 0.00 0.00 0.00 0.04	<u>%</u>	
Peak # 1 2 3 4 5 6 7 8 9 10	Ret Time 0.48 1.77 3.24 3.89 4.13 4.22 4.37 4.41 4.47 4.52	Area 0.00 0.04 0.00 99.56 0.10 0.05 0.00 0.00 0.00 0.04 0.19	<u>%</u>	
Peak # 1 2 3 4 5 6 7 8 9 10 11	Ret Time 0.48 1.77 3.24 3.89 4.13 4.22 4.37 4.41 4.47 4.52 5.30	Area 0.00 0.04 0.00 99.56 0.10 0.05 0.00 0.00 0.00 0.04 0.19 0.00	%	
Peak # 1 2 3 4 5 6 7 8 9 10 11 12	Ret Time 0.48 1.77 3.24 3.89 4.13 4.22 4.37 4.41 4.52 5.30 6.40	Area 0.00 0.04 0.00 99.56 0.10 0.05 0.00 0.00 0.00 0.04 0.19 0.00 0.00 0.00	%	

Peak 3 has been identified as Benzoylecgonine Peak 10 has been identified as Cocaethylene

GC/FID



Column:	DB-35m 1.0 µm	DB-35ms, 30 m x 0.53 mm ID, 1.0 um film thickness		
Temp Prog	r am: 40°C to	40°C to 200°C at 40°C/min		
	200°C t	o 300°C at 5°C/min		
	hold 16	min		
Injector Te	mp: Cool-on	-Column		
Detector Te	emp: 325°C			
Sample Nar	mo : FC1016	1002		
	March 1	0 2020		
Acquireu.		0, 2020		
Peak #	Ret Time	Area %		
1	4.18	0.00		
2	4.53	0.00		
3	4.68	0.00		
4	4.77	0.03		
5	4.91	0.01		
6	5.48	0.04		
7	7.06	0.01		
8	15.46	0.03		
9	16.07	99.64		
10	16.60	0.02		
11	16.73	0.21		
12	22.95	0.02		

Residual Solvent Analysis by GC/FID Headspace

FID1 A, (F-002-14-RMC-013 FC12161903 10.07mg.D)	Column:		DB-ALC1 30 m	x 0.53 mm,
Norm 1 0 0 200 -			3 µm film thicl	kness
- Herrich	Temp Pro	ogram:	40°C hold 12 r	nin to 220°C at
175-			40°C/min hold	5.5 min
150-	Carrier G	as:	Helium	
	Flow Rat	e:	2.0 mL/min	
125-	Detector	Heater Temp:	250°C	
	Injector:		Headspace Sar	npler
100-	HS Oven	Temp:	60°C	
75	Vial Equi	libration:	10 minutes	
50	Sample	lamo	FC101/1000	
~~.		ame.	FC12161903	
25-	Acquired	:	February 21, 2	020
0-	Peak	Compound	Area	Weight %
0 2.5 5 7.5 10 12.5 15 17.5 20 m	in 1	Ethyl ether	1474.88	0.64
	2	NMP	NA	NA
	Total			0.64



LC/MS



Isotopic Purity by LC/MS SIM



Stability

Short term stability studies have been performed in multiple storage conditions for a period of up to four weeks. Short term data is utilized 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 stability findings for this product is listed below.

Storage Condition	Mean Kinetic Temperature (MKT)	Time Period/Result	
Freezer	-15°C		
Refrigerator	4°C	No decrease in purity was noted afte	
Room Temperature	21°C	four weeks.	
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	April 20, 2020	Initial version.



Certified Reference Material - Certificate of Analysis

Cocaethylene, Primary Measurement Standard

[R-(exo,exo)-3-Benzoyloxy-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylic acid ethyl ester

Product No.:	C-010-1ML	Cerilliant Quality
Lot No.:	FE02202006	Cernindin Godiny
Description of CRM:	Cocaethylene in Acetonitrile (Solution)	ISO 17034
Expiration Date:	February 2025 See Section "Stability Assessment".	ISO/IEC 17025
Storage:	Store unopened in freezer (-10 °C to -25 °C).	ISO 13485
Shipping:	Ambient. See Section "Stability Assessment".	ISO 14001
Chemical formula:	$C_{18}H_{23}NO_4$ O_CH_3 H_3C_1	ISO 9001
CAS NO.: Bogulatory	USDEA Exampt Canadian TK # 61 1081	
Regulatory:		

Analyte		Certified Concentration \pm associated uncertainty U, u=k*u (k=2)	
Cocaethyle	ne	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 μ L for quantitative applications		
Instructions for handling and correct use: Health and safety information:	Concentration is corrected for chromatographic purity, residual water, 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. 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 17034 and registered testing laboratory AT-1352 according to ISO/IEC 17025.		



Darron Ellsworth, Quality Assurance Manager

April 16, 2020

Issue Date

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 17034 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.



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 17034, 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 calculated 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 are analytically 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-35ms 30 m x 0.53 mm ID, 1.0 μ m film thickness	Number of Points:	4
Temp Program:	60°C to 280°C at 40°C/min hold 7 min	Linearity (r) :	1.000
Injector Temp:	Cool-on-Column		
Detector Temp:	325°C		
	Varified Concentral		DCD Hemogeneity

		verified Concentration (mg/mL)	%KSD - Homogeneity	
Standard	Lot Number	Actual Reculta	Actual Besults	
Solution	Lot Number	Actual Results	Actual Results	
New Lot	FE02202006	1.004	0.2	
Previous Lot	FE09301903	1.001	0.2	

• 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: Material Lot:	Cocaethylene FC10141905	Chemical Form CAS Number: Molecular Weig	Iula: C ₁₈ H ₂₃ NO ₄ 529-38-4 ght: 317.38
	Material Characte	erization Summary	
Analytical Test		Method	Results
Primary Chromatograph	ic Purity by HPLC/UV Analysis	SP10-0102	99.9% ¹
Secondary Chromatographic Purity by GC/FID Analysis		SP10-0101	99.9% ²
Identity by LC/MS Analy	vsis	SP10-0107	Consistent with Structure
Identity by ¹ H-NMR Ana	lysis	USP <761>, SP10-0116	Consistent with Structure
Residual Solvent Analysi	is by GC/FID Headspace	AM1087 ³	0.37%
Residual Water Analysis by Karl Fischer Coulometry		AM1346 ³	Not Detected
Inorganic Content by Microash Analysis		SP10-0135	< 0.2%
Mass Balance Purity Fac	tor		99.51%

 $^{\rm 1}$ 0.12% Cocaine and no Benzoylecgonine detected by HPLC/UV analysis.

 $^{\rm 2}$ 0.10% Cocaine and no Benzoylecgonine detected by GC/FID analysis.

³ 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.

Spectral and Physical Data

HPLC/UV



Peak 1 is identified as Cocaine

GC/FID



Column:	DB-35ms, 30 m x 0.53 mm ID,	
1.0 μm film thickness		film thickness
Temp Progr	am: 40°C to	o 180°C at 40°C/min
	180°C	to 300°C at 5°C/min
	hold 12	.5 min
Injector Te	mp: Cool-or	n-Column
Detector Te	mp: 325°C	
Sample Name: FC10141905		1905
Acquired:	Acquired: January 21, 2020	
Peak #	Ret Time	Area %
1	16.38	0.10
2	16.64	0.03
3	17.11	99.87
Peak 1 is identified as Cocaine		

Residual Solvent Analysis by GC/FID Headspace



¹H NMR







Stability

Short term stability studies have been performed in multiple storage conditions for a period of up to four weeks. Short term data is utilized 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 stability findings for this product is listed below.

Storage Condition	Mean Kinetic Temperature (MKT)	Time Period/Result	
Freezer	-15°C		
Refrigerator	4°C	No decrease in purity was noted after four weeks.	
Room Temperature	21°C		
40°C	40°C		
Transport/Shipping: Stability studies support the transport of this product at ambient conditions.			
	I ame have atability has been assessed for	Energy stars as (10 00 to - 25 00)	

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	April 16, 2020	Initial version.


Certified Reference Material - Certificate of Analysis

Cocaeth	ylene-D ₈ , I	Primary Measurement Standard	Cerilliant Quality
3-Benzoyl-8-(trideuterometl	nyl)-8-azabicyclo	[3.2.1]octane-2-carboxylic pentadeuteroethyl ester	ISO 17034
Product No.:	C-025-1ML		ISO/IEC 17025
Lot No.:	FE03102005		ISO 13485
Description of CRM:	Cocaethylene-E	D ₈ in Acetonitrile (Solution)	ISO 14001
Retest Date:	June 2021	See Section "Stability Assessment".	ISO 9001
Storage:	Store unopened	d in freezer (-10 °C to -25 °C).	
Shipping:	Ambient.	See Section "Stability Assessment".	CD ₃
Chemical formula:	$C_{18}H_{15}D_8NO_4$	D ₃ C _N D	D
CAS No.:	152521-09-0)	
Regulatory:	USDEA Exempt		

Analyte	Certified Concentration ± associated uncertainty U, u=k*u (k=2)
Cocaethylene-D ₈	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	Concentration is corrected for chromatographic purity, residual water, residual solvents, and residual inorganics. No adjustment required before use.
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.
	For MS Applications, we advise laboratories not to mix lots during a single sequence.
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 17034 and registered testing laboratory AT-1352 according to ISO/IEC 17025.



Darron Ellsworth, Quality Assurance Manager

April 24, 2020

Issue Date

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 17034 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.



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 17034, 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 calculated 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 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			Calibration Curve		
Analysis Method:	HPLC/UV	Calibration Curve: Linear Regression		Linear Regression	
Column:	Ascentis Express Phenyl-Hexyl, 2.7 µm,		Number of I	Points:	4
	3.0 x 100 mm		Linearity (r)):	1.000
Mobile Phase:	Acetonitrile:0.1% Phosphoric acid in Water (35:65)				
Flow Rate:	1.5 mL/min				
Wavelength:	235 nm				
		Verified Concentration	n (mg/mL)	%	RSD - Homogeneity
Standard Solution	Lot Number	Actual Result	S		Actual Results
New Lot	FE03102005	0.995			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.

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: Material Lot:	Cocaethylene-D ₈ FC12181901	Chemical Forn CAS Number:	rula: C ₁₈ 152	H ₁₅ D ₈ NO ₄ 2521-09-0
		Molecular Wei	ght: 325	.43
	Material Characte	erization Summary		
Analytical Test		Method	Results	
Primary Chromatographi	c Purity by HPLC/UV Analysis	20384348	99 .8% ¹	
Secondary Chromatogra	phic Purity by GC/FID Analysis	20384346	99.	9%
Identity by LC/MS Analysis		20384217	Consistent with Structure	
			0.00%	D ₀ vs D ₈
Isotopic Purity and Distribution by LC/MS SIM Analysis			0.00% D_0 to D_1	0.02% D_5 to D_6
		20384217	0.03% D ₂	1.97% D ₇
			0.01% D ₃	97.95% D ₈
			0.00% D ₄	
Identity by ¹ H-NMR Analysis		20384224	Consistent with Structure	
Residual Solvent Analysis by GC/FID Headspace		20397799 ²	0.19%	
Residual Water Analysis by Karl Fischer Coulometry		20398075 ²	Not Detected	
Inorganic Content by Microash Analysis		20384350	< 0.2%	
Mass Balance Purity Factor			99.	60%

 1 < 0.01% Benzoylecgonine-D₈ and 0.03% Cocaine-D₈ detected by HPLC/UV analysis.

² 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.

Spectral and Physical Data

HPLC/UV



5

6

3.58

4.14

0.06

0.00

GC/FID



Column:	DB-35n	ns, 30 m x 0.53 m	וm ID,
Temp Progra	am: 40°C tc 200°C t hold 18	40°C to 200°C at 40°C/min 200°C to 280°C at 5°C/min hold 18 min	
Injector Ter	np: Cool-or	n-Column	
Detector Ter	mp: 325°C		
Sample Nam Acquired:	ne: FC1218 March 7	FC12181901 March 14, 2020	
Peak #	Ret Time	Area %	
1	4.62	0.00	
2	4.73	0.00	
3	13.00	0.02	
4	13.17	0.04	
5	13.59	99.92	

0.01

14.09

6





¹H NMR



LC/MS



Isotopic Purity by LC/MS SIM



Cerilliant Corporation, 811 Paloma Drive, Suite A Round Rock, f 10 TX 78665, USA, Tel: 800-848-7837 / 512-238-9974

Certificate Page 9 of 10

Stability

Short term stability studies have been performed in multiple storage conditions for a period of up to four weeks. Short term data is utilized 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 stability findings for a related product (C-010, Cocaethylene) is listed below.

Storage Condition	Mean Kinetic Temperature (MKT)	Time Period/Result	
Freezer	-15°C		
Refrigerator	4°C	No decrease in purity was noted after	
Room Temperature 21°C		four weeks.	
40°C	40°C		
Transport/Shipping: Stability studies support the transport of this product at ambient conditions.			

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	April 24, 2020	Initial version.



Certified Reference Material - Certificate of Analysis

Dip	henhydramine, Primary Measurement Standard	Cerilliant Quality
	2-(Diphenylmethoxy)-N,N-dimethylethylamine hydrochloride	ISO 17034
Product No.:	D-015-1ML	100 /150 17005
Lot No.:	FN02212010	ISO/IEC 17025
Description of CRM	1: Diphenhydramine HCl in Methanol (Solution)	ISO 13485
	Nominal concentration is adjusted for HCl content.	ISO 14001
Expiration Date:	March 2025 See Section "Stability Assessment".	ISO 9001
Storage:	Store unopened in freezer (-10 °C to -25 °C).	CH
Shipping:	Ambient. See Section "Stability Assessment".	L ●HCI
Chemical formula:	C ₁₇ H ₂₁ NO • HCl	^{_N} _CH₃
CAS No.:	147-24-0	

Analyte	Certified Concentration \pm associated uncertainty U, $u=k*u$ (k=2)	
Diphenhydramine	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 μ L for quantitative applications
Instructions for handling and correct use:	Concentration is corrected for chromatographic purity, residual water, 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. Nominal concentration is adjusted for HCl content. No adjustment required before 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 17034 and registered testing laboratory AT-1352 according to ISO/IEC 17025.



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Darron Ellsworth, Quality Assurance Manager

April 06, 2020

Issue Date

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 17034 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.



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 17034, 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 calculated 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 are analytically 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:	HPLC/UV	Calibration Curve:	Linear Regression
Column:	Ascentis Express Phenyl Hexyl, 2.7 μm, 3.0 x 50 mm	Number of Points:	: 4
Mobile Phase:	Acetonitrile:0.1% Phosphoric acid in Water (25:75)	Linearity (r) :	1.000
Flow Rate:	1.2 mL/min		
Wavelength:	220 nm		
	Verified Concentration	on (mg/ml) °	%RSD - Homogeneity

		Vernica concentration (mg/me)	/ited fields
Standard Solution	Lot Number	Actual Results	Actual Results
New Lot	FN02212010	0.999	0.3
Previous Lot	FN11091601	0.997	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.

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 and salt adjustment are utilized to calculate the weighing adjustment necessary to ensure accuracy of the solution standard concentration.

Material Name: Material Lot: Chemical Formula: CAS Number:	Diphenhydramine HCl PN12191901 C ₁₇ H ₂₁ NO • HCl 147-24-0	Molecular Weig Molecular Weig Salt Adjustme	ght (base):255.35ght (salt):291.82nt:1.143	
	Material Characte	erization Summary		
Analytical Test		Method	Results	
Primary Chromatographic	Purity by HPLC/UV Analysis	20384348	99.9%	
Secondary Chromatographic Purity by GC/FID Analysis		20384346	> 99.9%	
Identity by LC/MS Analysis		20384217	Consistent with Structure	
Identity by ¹ H-NMR Analysis		20384224	Consistent with Structure	
Residual Solvent Analysis by GC/FID Headspace		20397799 ¹	None Detected	
Residual Water Analysis by Karl Fischer Coulometry		20398075 ¹	Below Quantitation Limit	
Inorganic Content by Microash Analysis		20384350	< 0.2%	
Mass Balance Purity Factor			99.86%	

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.

Spectral and Physical Data

HPLC/UV



Column:	Ascentis E	xpress Ph	ienyl-He	exyl,
Mobile Phase:	A: Aceton	itrile		
	B: 0.1% P	hosphoric	acid in	Water
Gradient:	Time (min)%A	% B	
	0.0	10	90	•
	8.0	75	25	
	10.0	75	25	
	10.1	10	90	
Flow Rate:	0.7 mL/m	in		
Wavelength:	220 nm			
Sample Name	PN121919	01		
Acquired:	January 2	3, 2020		
Book # B	ot Timo	Aroz 0/2		
1 Peak # R	2 2E	Area %	<u> </u>	
1	3.23	0.01		
2	3.05	0.01		
7	4.40	0.00		
4	4.45	0.01		
5	4.02 5 1 0	0.01		
0	5.12	0.02		
2 2	5.20	0.01		
0	6.52	0.02		
10	6.92	0.01		

GC/FID



٦	Column:	DB-35r	ms, 30 m x 0.53 mm ID,
	Temp Pro <u>c</u>	gram: 40°C to 140°C hold 5	o 140°C at 40°C/min to 280°C at 5°C/min min
	Injector To	emp: Cool-or	n-Column
	Detector T	emp: 325°C	
	Sample Na	me: PN1219	91901
	Acquired:	Januar	y 23, 2020
	Peak #	Ret Time	Area %
	1	15.12	99.98
	2	16.29	0.00
	3	16.66	0.00
	4	17.75	0.00
_	5	18.25	0.01
Ļ	6	18.55	0.00

0.00

23.58

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Residual Solvent Analysis by GC/FID Headspace



¹H NMR





Stability

Short term stability studies have been performed in multiple storage conditions for a period of up to four weeks. Short term data is utilized 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 stability findings for this product is listed below.

Storage Condition	Mean Kinetic Temperature (MKT)	Time Period/Result
Freezer	-15°C	
Refrigerator	4°C	No decrease in purity was noted after
Room Temperature	21°C	four weeks.
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	April 06, 2020	Initial version.



Certified Reference Material - Certificate of Analysis

Dipher	nhydramine-D ₃ , Primary Measurement Standard	Cerilliant Quality
	2-(Diphenylmethoxy)-N-methyl-N-(trideuteromethyl)ethylamine	ISO 17034
Product No.:	D-187-1ML	ISO/IEC 17025
Lot No.:	FN04082007	ISO 13485
Description of CRM:	Diphenhydramine-D ₃ in Methanol (Solution)	ISO 14001
Expiration Date:	April 2025 See Section "Stability Assessment".	150 9001
Storage:	Store unopened in freezer (-10 °C to -25 °C).	3
Shipping:	Ambient. See Section "Stability Assessment".	ı
Chemical formula:	$C_{17}H_{18}D_3NO$	
CAS No.:	170082-18-5	

Analyte	Certified Concentration ± associated uncertainty U, u=k*u (k=2)
Diphenhydramine-D ₃	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 water, 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. For MS Applications, we advise laboratories not to mix lots during a single sequence.
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 17034 and registered testing laboratory AT-1352 according to ISO/IEC 17025.



Darron Ellsworth, Quality Assurance Manager

Мау 06, 2020

Issue Date

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 17034 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.



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 17034, 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 calculated 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 are analytically verified against an independently prepared calibration solution and to the prior lot.

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

Standard Solution Assay Parameters			Calibration Curve		
Analysis Method:	HPLC/UV		Calibration	Curve:	Linear Regression
Column:	Ascentis Express Phenyl-Hexyl, 2.7 µm,		Number of Points: 4		4
	3.0 x 100 mm		Linearity (r):	1.000
Mobile Phase: Flow Rate:	Acetonitrile:0.1% P (40:60) 1.2 mL/min	hosphoric acid in Water			
Wavelength:	220 nm				
		Verified Concentration	(mg/mL)	%F	SD - Homogeneity
Standard Solution	Lot Number	Actual Result	s		Actual Results
New Lot	FN04082007	1.000			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.

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 and salt adjustment are utilized to calculate the weighing adjustment necessary to ensure accuracy of the solution standard concentration.

Material Name:	Diphenhydramine-D ₃	Chemical Form	nula:	ula: C ₁₇ H ₁₈ D ₃ NO	
Material Lot:	FN10041909	CAS Number:	170082-18-5		082-18-5
		Molecular Weig	ght:	258	.37
	Material Charact	erization Summary			
Analytical Test		Method		Res	ults
Primary Chromatographic	c Purity by HPLC/UV Analysis	20384348		99.	6%
Secondary Chromatographic Purity by LC/MS Analysis		20384217		> 99	9.9%
Identity by LC/MS Analys	is	20384217	Consist	tent w	ith Structure
			0.	01% I	D ₀ vs D ₃
Isotopic Purity and Distril	bution by LC/MS SIM Analysis	20384217	0.01%	D ₀	2.95% D ₂
			0.04%	D ₁	97.01% D ₃
Identity by ¹ H-NMR Analy	ysis	20384224	Consistent with Structure		ith Structure
Residual Solvent Analysis	s by GC/FID Headspace	20397799 ¹	Below Quantitation Limit		titation Limit
Residual Water Analysis by Karl Fischer Coulometry		20398075 ¹	0.16%		6%
Mass Balance Purity Facto	or			99.4	10%

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.

Spectral and Physical Data

HPLC/UV



Column:	Ascentis	s Express Ph	nenyl-He	xyl,
	2.7 μm,	3.0 x 100 ı	mm	
Mobile Phas	se: A: Acete	onitrile		
	B: 0.1%	5 Phosphoric	c acid in	Wate
Gradient:	Time (m	nin) %A	% B	
	0.0	10	90	
	8.0	75	25	
	10.0	75	25	
	10.1	10	90	
Flow Rate:	0.7 mL/	min		
Wavelength	n: 220 nm			
Sample Nar	ne: FN1004	1909		
Acquired:	March C	5, 2020		
Peak #	Dot Time	Ama = 0/		
I Cak #	Ret Time	Area %		
1	4.72	0.04		
1 2	4.72 4.76	0.04 99.59		
1 2 3	4.72 4.76 5.11	0.04 99.59 0.02		
1 2 3 4	4.72 4.76 5.11 5.19	0.04 99.59 0.02 0.03		
1 2 3 4 5	4.72 4.76 5.11 5.19 5.39	0.04 99.59 0.02 0.03 0.01		
1 2 3 4 5 6	4.72 4.76 5.11 5.19 5.39 5.47	0.04 99.59 0.02 0.03 0.01 0.02		
1 2 3 4 5 6 7	4.72 4.76 5.11 5.19 5.39 5.47 5.56	0.04 99.59 0.02 0.03 0.01 0.02 0.01		
1 2 3 4 5 6 7 8	4.72 4.76 5.11 5.19 5.39 5.47 5.56 5.74	0.04 99.59 0.02 0.03 0.01 0.02 0.01 0.02		
1 2 3 4 5 6 7 8 9	4.72 4.76 5.11 5.19 5.39 5.47 5.56 5.74 5.84	0.04 99.59 0.02 0.03 0.01 0.02 0.01 0.02 0.01		
1 2 3 4 5 6 7 8 9 10	4.72 4.76 5.11 5.19 5.39 5.47 5.56 5.74 5.84 5.92	0.04 99.59 0.02 0.03 0.01 0.02 0.01 0.02 0.01 0.01		
1 2 3 4 5 6 7 8 9 10 11	4.72 4.76 5.11 5.19 5.39 5.47 5.56 5.74 5.84 5.84 5.92 6.16	0.04 99.59 0.02 0.03 0.01 0.02 0.01 0.02 0.01 0.01 0.01 0.12		
1 2 3 4 5 6 7 8 9 10 11 12	4.72 4.76 5.11 5.19 5.39 5.47 5.56 5.74 5.84 5.92 6.16 6.41	0.04 99.59 0.02 0.03 0.01 0.02 0.01 0.02 0.01 0.01 0.01 0.12 0.04		
1 2 3 4 5 6 7 8 9 10 11 12 13	Ket fille 4.72 4.76 5.11 5.19 5.39 5.47 5.56 5.74 5.84 5.92 6.16 6.41 6.54	0.04 99.59 0.02 0.03 0.01 0.02 0.01 0.02 0.01 0.01 0.12 0.04 0.02		
1 2 3 4 5 6 7 8 9 10 11 12 13 14	4.72 4.76 5.11 5.19 5.39 5.47 5.56 5.74 5.84 5.92 6.16 6.41 6.54 6.66	0.04 99.59 0.02 0.03 0.01 0.02 0.01 0.02 0.01 0.01 0.12 0.04 0.02 0.01		
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15	4.72 4.76 5.11 5.19 5.39 5.47 5.56 5.74 5.84 5.92 6.16 6.41 6.54 6.66 7.09	0.04 99.59 0.02 0.03 0.01 0.02 0.01 0.02 0.01 0.02 0.01 0.12 0.04 0.02 0.01 0.02		

Residual Solvent Analysis by GC/FID Headspace



¹H NMR



Certificate Page 7 of 10

Cerilliant Corporation, 811 Paloma Drive, Suite A Round Rock, TX 78665, USA, Tel: 800-848-7837 / 512-238-9974

LC/MS



Isotopic Purity by LC/MS SIM



Stability

Short term stability studies have been performed in multiple storage conditions for a period of up to four weeks. Short term data is utilized 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 stability findings for this product is listed below.

Storage Condition	Mean Kinetic Temperature (MKT)	Time Period/Result
Freezer	-15°C	
Refrigerator	4°C	No decrease in purity was noted after
Room Temperature	21°C	four weeks.
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	May 06, 2020	Initial version.



Certified Reference Material - Certificate of Analysis

Diazo	epam, Primary Measurement Standard	Cerilliant Quality
7-Chloro-	1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one	ISO 17034
Product No.:	D-907-1ML	ISO/IEC 17025
Lot No.:	FE02142004	ISO 13485
Description of CRM:	Diazepam in Methanol (Solution)	150 14001
Expiration Date:	February 2025 See Section "Stability Assessment".	130 14001
Storage:	Store unopened in freezer (-10 °C to -25 °C).	ISO 9001
Shipping:	Ambient. See Section "Stability Assessment".	
Chemical formula:	C ₁₆ H ₁₃ ClN ₂ O	>
CAS No.:	439-14-5	
Regulatory:	USDEA Exempt Canadian TK # 61-1156	м—сн ₃ ∕

Analyte		Certified Concentration \pm associated uncertainty U, $u=k*u$ (k=2)	
Diazepan	ı	1.000 ± 0.006 mg/mL	
Metrological traceability:	Traceable to the S unbroken chain o page 2.	SI and higher order standards from NIST through an f comparisons. See "Details on metrological traceability" on	
Measurement method:	The certified valu characterized star page 2.	e is calculated from high precision weighing of thoroughly ting material. See "Details about certification process" on	
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 μ L for quantitat	1 μ L for quantitative applications	
Instructions for handling and correct use: Health and safety	Concentration is of solvents, and residusers should quar laboratory practic concentration. Ea Danger. Please residue and provide and provi	corrected for chromatographic purity, residual water, residual dual inorganics. No adjustment required before use. ntitatively transfer desired volume using established good tes to spike into matrix or to dilute to the desired ch ampoule is intended for one-time use. Ifer to the Safety Data Sheet for detailed information about	
information:	the nature of any	hazard and appropriate precautions to be taken.	
Accreditation:	Cerilliant Corp. is registered referent and registered test	accredited by the US accreditation authority ANAB as acce material producer AR-1353 in accordance with ISO 17034 sting laboratory AT-1352 according to ISO/IEC 17025.	



Darron Ellsworth, Quality Assurance Manager

March 11, 2020

Issue Date

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 17034 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.



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 17034, 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 calculated 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 are analytically 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:	HPLC/UV	Calibration Curve:	Linear Regression
Column:	Ascentis Express Phenyl-Hexyl, 2.7 μm, 3.0 x 50 mm	Number of Points:	4
Mobile Phase:	Acetonitrile:Water (50:50)	Linearity (r) :	1.000
Flow Rate:	1.0 mL/min		
Wavelength:	238 nm		

		Verified Concentration (mg/mL)	%RSD - Homogeneity
Standard Solution	Lot Number	Actual Results	Actual Results
New Lot	FE02142004	1.004	0.7
Previous Lot	FE05201602	1.006	1.0

• 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: Material Lot:	Diazepam PC10141901	Chemical Form CAS Number: Molecular Weig	ula: C ₁₆ H ₁₃ ClN ₂ O 439-14-5 ht: 284.74
	Material Characteri	zation Summary	
Analytical Test		Method	Results
Primary Chromatographi	c Purity by HPLC/UV Analysis	20384348	> 99.9%
Secondary Chromatograp	phic Purity by GC/FID Analysis	20384346	> 99.9%
Identity by LC/MS Analys	sis	20384217	Consistent with Structure
Identity by ¹ H-NMR Analy	ysis	20384224	Consistent with Structure
Residual Solvent Analysis	s by GC/FID Headspace	20397799 ¹	None Detected
Residual Water Analysis	by Karl Fischer Coulometry	20398075 ¹	Not Detected
Inorganic Content by Mic	roash Analysis	20384350	< 0.2%
Mass Balance Purity Fact	or		99.99%

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.

Spectral and Physical Data

HPLC/UV



Column:	Ascentis	Ascentis Express Phenyl-Hexyl,		
	2.7 µm	, 3.0 x 50 r	nm	
Mobile Pha	se: A: Aceto	onitrile		
	B: Wate	er		
Gradient:	Time (m	nin) %A	% B	
	0.0	30	70	
	4.0	85	15	
	5.0	85	15	
	5.1	30	70	
Flow Rate:	0.8 mL/	min		
Wavelengtl	h: 238 nm			
Sample Na	me: PC1014	1901		
Acquired:	January	07, 2020		
Peak #	Ret Time	Area %)	
1	1.90	0.00		
2	2.26	0.00		
3	2.40	99.99		
4	2.80	0.00		

0.00

3.02

GC/FID



Column:	DB-5	ms, 30 m x 0.53 mm II	D,
	1.5 µ	m film thickness	
Temp Prog	ram: 40°C	to 200° C at 40° C/min	
	bold	16 min	
Iniector Te	mp: Cool-	on-Column	
Detector To	emp: 325°	C	
Sample Na	me: PC10	PC10141901	
Acquired:	Janua	January 14, 2020	
Peak #	Ret Time	Area %	
1	14.40	0.01	
2	15.07	0.01	
3	15.41	99.98	

5

Residual Solvent Analysis by GC/FID Headspace




LC/MS



Stability

Short term stability studies have been performed in multiple storage conditions for a period of up to four weeks. Short term data is utilized 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 stability findings for a related product (D-902, Diazepam- D_5) is listed below.

Storage Condition	Mean Kinetic Temperature (MKT)	Time Period/Result		
Freezer	-15°C			
Refrigerator	4°C	No decrease in purity was noted after		
Room Temperature	21°C	four weeks.		
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	March 11, 2020	Initial version.



Certified Reference Material - Certificate of Analysis

Diazepam-D₅, Primary Measurement Standard

7-Chloro-1,3-dihydro-1-methyl-5-(pentyl-2,3,4,5,6-d 5)-2H-1,4-benzodiazepin-2-one

Product No.:	D-910-1ML	Cerilliant Quality
Lot No.:	FE01142012	ISO 17034
Description of CRM:	Diazepam-D ₅ in Methanol (Solution)	ISO/IEC 17025
Expiration Date:	January 2025 See Section "Stability Assessment".	150 13485
Storage:	Store unopened in freezer (-10 °C to -25 °C).	130 13405
Shipping:	Ambient. See Section "Stability Assessment".	ISO 14001
Chemical formula:	$C_{16}H_8D_5CIN_2O$	ISO 9001
CAS No.:	65854-76-4 CI	
Regulatory:	USDEA Exempt Canadian TK # 61-1157	

Analyte		Certified Concentration \pm associated uncertainty U, $u=k*u$ (k=2)	
Diazepam-	D ₅	1.000 ± 0.006 mg/mL	
Metrological traceability:	Traceable to the S unbroken chain of page 2.	SI and higher order standards from NIST through an f comparisons. See "Details on metrological traceability" on	
Measurement method:	The certified value characterized star page 2.	e is calculated from high precision weighing of thoroughly tring material. See "Details about certification process" on	
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 μ L for quantitat	ive applications	
Instructions for handling and correct use:	Concentration is of solvents, and resi Users should quar laboratory practic concentration. Ea For MS Application sequence.	corrected for chromatographic purity, residual water, residual dual inorganics. No adjustment required before use. ntitatively transfer desired volume using established good tes to spike into matrix or to dilute to the desired ch ampoule is intended for one-time use. ns, we advise laboratories not to mix lots during a single	
Health and safety information:	Danger. Please re the nature of any	fer to the Safety Data Sheet for detailed information about hazard and appropriate precautions to be taken.	
Accreditation:	Cerilliant Corp. is registered referen and registered tes	accredited by the US accreditation authority ANAB as accematerial producer AR-1353 in accordance with ISO 17034 sting laboratory AT-1352 according to ISO/IEC 17025.	



February 25, 2020

Darron Ellsworth, Quality Assurance Manager

Issue Date

D D

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 17034 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.



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 17034, 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 calculated 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 are analytically 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 Paran	neters		C	Calibration Cu	rve	
Analysis Method:	HPLC/UV	HPLC/UV				Calibration Curve: Linear Regres	
Column:	Ascentis Express C18, 2.7 µm, 3.0 x 50 mm				Number of Poi	nts:	4
Mobile Phase:	A: Acetonitri B: Water	le		L	inearity (r) :		1.000
Gradient:	Time (min)	% A	% B				
	0.00	30	70				
	4.50	70	30				
	5.50	70	30				
	5.51	30	70				
	8.00	30	70				
Flow Rate:	0.8 mL/min						
Wavelength:	238 nm						
			Verifi	ed Concentration ((mg/mL)	%F	SD - Homogeneity
Standard Solution	Lot Num	ber		Actual Results			Actual Results
New Lot	FE01142	012		0.998			2.0
Previous Lot	FE08011	803		1.009			2.1

• 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: Material Lot:	Diazepam-D₅ FC02201702	Chemical Forn CAS Number: Molecular Wei	nula: C ₁₆ h 658 ght: 289	H ₈ D₅CIN₂O 54-76-4 .77
	Material Charact	erization Summary		
Analytical Test		Method	Res	ults
Primary Chromatographi	ic Purity by HPLC/UV Analysis	SP10-0102	99.6	5% ¹
Secondary Chromatogra	phic Purity by GC/FID Analysis	SP10-0101	99.	8%
Identity by LC/MS Analy	sis	SP10-0107	Consistent with Structure	
			0.00%	D ₀ vs D ₆
Isotopic Purity and Dist	ribution by LC/MS		0.00% D_0 to D_2	95.75% D ₅
SIM Analysis		SP10-0107	0.01% D ₃	0.40% D ₆
			1.57% D ₄	2.28% D ₇
Identity by ¹ H-NMR Anal	lysis	USP <761>, SP10-0116	Consistent w	ith Structure
Residual Solvent Analysi	is by GC/FID Headspace	AM1087 ²	0.40%	
Residual Water Analysis	by Karl Fischer Coulometry	AM1346 ²	Not Detected	
Inorganic Content by Mi	croash Analysis	SP10-0135	< 0.2%	
Mass Balance Purity Fac	tor		99.1	18%

¹ 0.01% Nordiazepam-D5 detected by HPLC/UV analysis.

² 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.

Spectral and Physical Data

HPLC/UV



Peak 1 identified as Nordiazepam-D₅

4.71

0.08

6

GC/FID



Column:	DE	3-5ms, 30 m x 0.53 mm ID,	
	1.	5 µm film thickness	
Temp Prog	gram: 40	P°C to 200°C at 40°C/min	
	20	00°C to 300°C at 5°C/min	
	hc	ld 16 min	
Injector T	emp: Co	ool-on-Column	
Detector 1	emp: 32	25°C	
Sample Na	ame: FC	02201702	
Acquired:	Ap	April 19, 2017	
Peak #	Ret Time	Area %	
1	15.53	99.78	
2	16.91	0.08	
3	25.73	0.05	
4	27.58	0.09	

Residual Solvent Analysis by GC/FID Headspace





LC/MS

Column: Mobile Phase:	Ascentis E A: 0.1% F B: Acetoni	xpress ormic a trile	C18, 2.7 µm, 3.0 x 50 mm acid in Water	Flow Rate: 0.4 m Scan Range: 100 - Ionization: Electri Instrument: Wate	0.4 mL/min 100 - 1200 amu Electrospray, Positive Ion
	0.0 5.0 6.0	70 40 40	30 60 60	Instrument: Acquired:	Waters XEVO G2 QTOF April 13, 2017
	6.1 8.0	70 70	30 30		



Isotopic Purity and Distribution by LC/MS





Stability

Short term stability studies have been performed in multiple storage conditions for a period of up to four weeks. Short term data is utilized 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 stability findings for this product is listed below.

Storage Condition	Mean Kinetic Temperature (MKT)	Time Period/Result		
Freezer	-15°C			
Refrigerator	4°C	No decrease in purity was noted after		
Room Temperature	21°C	four weeks.		
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	February 25, 2020	Initial version.



Certified Reference Material - Certificate of Analysis

Ecgonine, Primary Measurement Standard

[1R-(exo,exo)]-3-hydroxy-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylic acid hydrochloride

Product No.:	E-004-1ML	Cerilliant Quality
Lot No.:	FE03232001	ISO 17034
Description of CRM:	Ecgonine HCl in Methanol (Solution)	ISO/IEC 17025
	Nominal concentration is adjusted for HCI content.	150 12495
Expiration Date:	March 2025 See Section "Stability Assessment".	150 13485
Storage:	Store unopened in freezer (-10 °C to -25 °C).	ISO 14001
Shipping:	Ambient. See Section "Stability Assessment".	ISO 9001
Chemical formula:	C ₉ H ₁₅ NO ₃ • HCl	
CAS No.:	5796-31-6 H ₂ C ^{-N} OH	
Regulatory:	USDEA Exempt Canadian TK # 61-1165	

Analyte	Certified Concentration \pm associated uncertainty U, u=k*u (k=2)
Ecgonine	$1.000 \pm 0.006 \text{ mg/mL}$

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 water, 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. Nominal concentration is adjusted for HCl content. No adjustment required before 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 17034 and registered testing laboratory AT-1352 according to ISO/IEC 17025.



Darron Ellsworth, Quality Assurance Manager

May 06, 2020

Issue Date

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 17034 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.



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 17034, 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 calculated 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 are analytically 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:	LC/MS	Calibration Curve	Linear Regression
Column:	Ascentis Express F5, 3 µm, 2.7 x 100 mm	Number of Points	: 4
Mobile Phase: Flow Rate:	0.1% Formic acid in Water:Acetonitrile (99:1) 0.4 mL/min	Linearity (r) :	0.998
Polarity:	MRM, Positive Ion		
	Verified Concentration	(mg/mL)	%RSD - Homogeneity

		vermed concentration (ing/inc)	%KSD - Holliogeneity
Standard Solution	Lot Number	Actual Results	Actual Results
New Lot	FE03232001	0.985	0.5
Previous Lot	FE01221901	0.998	1.4

• 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 and salt adjustment are utilized to calculate the weighing adjustment necessary to ensure accuracy of the solution standard concentration.

Material Name: Material Lot: Chemical Formula: CAS Number:	Ecgonine HCl FC10141904 C ₉ H ₁₅ NO ₃ • HCl 5796-31-6	Molecular Weig Molecular Weig Salt Adjustmen	Jht (base):185.22Jht (salt):221.68It:1.197	
	Material Charact	erization Summary		
Analytical Test		Method	Results	
Primary Chromatographic	Purity by GC/FID Analysis	SP10-0101	99.8%	
Secondary Chromatographic Purity by LC/MS Analysis		SP10-0107	> 99.9%	
Identity by LC/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 Level	
Inorganic Content by Microash Analysis		SP10-0135	< 0.2%	
Mass Balance Purity Factor			99.76%	

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.

Spectral and Physical Data

GC/FID



Column:	DB-5m	ms, 30 m x 0.53 mm ID	
	1.5 µm	film thickness	
Temp Progr	am: 40°C to	180°C at 40°C/min	
	180°C 1	to 280°C at 5°C/min	
	hold 5 i	min	
Injector Te	mp: Cool-or	n-Column	
Detector Te	mp: 325°C		
Sample Nar	ne: FC1014	1904	
Acquired:	January	January 10, 2020	
Peak #	Ret Time	Area %	
1	18.76	0.02	
2	19.57	0.03	
3	20.42	99.78	
4	25.66	0.03	
5	26.26	0.01	

0.01

0.02

0.01

0.01 0.02

0.01 0.01

0.02

0.02

27.27

27.81

28.46

29.26

29.80

30.30

31.66 33.46

35.43

Residual Solvent Analysis by GC/FID Headspace

Residual Solvent Analysis by GC/11D fiead	ispace	
FID1 A, (F-002-12-RME-002 FC10141904 13.57mg.D)	Column:	DB-ALC1 30 m x 0.53 mm,
Norm.]		3 µm film thickness
	Temp Program:	40°C hold 12 min to 220°C at
175-		40°C/min hold 5.5 min
	Carrier Gas:	Helium
150-	Flow Rate:	2.0 mL/min
	Detector Heater Temp	: 250°C
125-	Injector:	Headspace Sampler
	HS Oven Temp:	60°C
100-	Vial Equilibration:	10 minutes
75-	Sample Name:	FC10141904
50-	Acquired:	January 16, 2020
25-	Peak Compound	Area Weight %
	1 NMP	NA NA
0-	Total	ND
0 25 5 7.5 10 12.5 15 17.5 20	mir	ND - None Detected

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LC/MS



Stability

Short term stability studies have been performed in multiple storage conditions for a period of up to four weeks. Short term data is utilized 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 stability findings for a related product (E-003, Ecgonine-D₃ HCl) is listed below.

Storage Condition	Mean Kinetic Temperature (MKT)	Time Period/Result
Freezer	-15°C	
Refrigerator	4°C	No decrease in purity was noted after
Room Temperature	21°C	four weeks.
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	May 06, 2020	Initial version.



Certified Reference Material - Certificate of Analysis

Ecgonine-D₃, Primary Measurement Standard

[1R-(exo,exo)]-3hydroxy-8-(trideuteromethyl)-8-azabicyclo[3.2.1]octane-2-carboxylic acid hydrochloride

Product No.:	E-010-1ML	Cerilliant Quality
Lot No.:	FE03192003	ISO 17034
Description of CRM:	Ecgonine-D ₃ HCI in Methanol (Solution)	ISO/IEC 17025
	Nominal concentration is adjusted for HCI content.	ISO 13485
Retest Date:	July 2021 See Section "Stability Assessment".	ISO 14001
Storage:	Store unopened in freezer (-10 °C to -25 °C).	
Shipping:	Ambient. See Section "Stability Assessment". O ₅ ,OH	
Chemical formula:	$C_9H_{12}D_3NO_3 \bullet HCI$	
CAS No.:	115144-41-7 D ₃ C-N O	HCI
Regulatory:	USDEA Exempt	-

Analyte		Certified Concentration ± associated uncertainty U, u=k*u (k=2)
Ecgonine-L	D ₃	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 water, 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. Nominal concentration is adjusted for HCI content. No adjustment required before use. For MS Applications, we advise laboratories not to mix lots during a single	
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 registered referen and registered tes	accredited by the US accreditation authority ANAB as accredited producer AR-1353 in accordance with ISO 17034 sting laboratory AT-1352 according to ISO/IEC 17025.



June 05, 2020

Darron Ellsworth, Quality Assurance Manager

Issue Date

Cerilliant Corporation, 811 Paloma Drive, Suite A Round Rock, TX 78665, USA, Tel: 800-848-7837 / 512-238-9974 E-010-1ML Revision 00

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 17034 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.



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 17034, 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 calculated 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 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		Calibration Curve	
Analysis Method:	LC/MS	Calibration Curve:	Linear Regression
Column:	Ascentis Express C18, 2.7 µm, 3.0 x 100 mm	Number of Points:	4
Mobile Phase:	0.1% Formic acid in Water: Acetonitrile (99:1)	Linearity (r) :	1.000
Flow Rate:	0.4 mL/min		
Polarity: MRM, Positive Ion			
	Varified Concentration		

Ve		Verified Concentration (mg/mL)	%RSD - Homogeneity
Standard Solution	Lot Number	Actual Results	Actual Results
New Lot	FE03192003	0.995	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.

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 and salt adjustment are utilized to calculate the weighing adjustment necessary to ensure accuracy of the solution standard concentration.

Material Name: Material Lot:	Ecgonine-D₃ HCl FC12161904	Molecular Weig Molecular Weig	ght (base):	188.24 224.70
Chemical Formula:	$C_0H_{12}D_3NO_3 \bullet HCI$	Salt Adjustmer	nt:	1.194
CAS Number:	115144-41-7	· · · · · · · · · · · · · · · · · · ·		
	Material Charact	erization Summary		
Analytical Test		Method	Res	sults
Primary Chromatographic	Purity by GC/FID Analysis	SP10-0101	99	4%
Secondary Chromatograph	nic Purity by LC/MS Analysis	SP10-0107	> 99	9.9%
Identity by LC/MS Analysis		SP10-0107	Consistent with Structure	
			0.02%	D ₀ vs D ₃
Isotopic Purity and Distribution by LC/MS SIM Analysis		SP10-0107	0.02% D ₀	0.28% D ₂
			0.01% D ₁	99.68% D ₃
Identity by ¹ H-NMR Analysis		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.	40%

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.

Spectral and Physical Data

GC/FID



Column:	DB-5m	ns, 30 m x 0.53 mm ID,
	1.5 µm	n film thickness
Temp Prog	gram: 40°C t	o 80°C at 40°C/min
	80°C t	o 200°C at 5°C/min
	200°C	to 280°C at 40°C/min
	hold 10	0 min
Injector T	emp: Cool-o	n-Column
Detector T	emp: 325°C	
Sample Na	me: FC121	61904
Acquired:	April 0	6, 2020
Peak #	Ret Time	Area %
Peak #	Ret Time 18.50	Area %
Peak # 1 2	Ret Time 18.50 19.29	Area % 0.02 0.08
Peak # 1 2 3	Ret Time 18.50 19.29 20.15	Area % 0.02 0.08 99.17
Peak # 1 2 3 4	Ret Time 18.50 19.29 20.15 25.28	Area % 0.02 0.08 99.17 0.37
Peak # 1 2 3 4 5	Ret Time 18.50 19.29 20.15 25.28 25.49	Area % 0.02 0.08 99.17 0.37 0.03
Peak # 1 2 3 4 5 6	Ret Time 18.50 19.29 20.15 25.28 25.49 25.57	Area % 0.02 0.08 99.17 0.37 0.03 0.01
Peak # 1 2 3 4 5 6 7	Ret Time 18.50 19.29 20.15 25.28 25.49 25.57 26.46	Area % 0.02 0.08 99.17 0.37 0.03 0.01 0.15
Peak # 1 2 3 4 5 6 7 8	Ret Time 18.50 19.29 20.15 25.28 25.49 25.57 26.46 27.33	Area % 0.02 0.08 99.17 0.37 0.03 0.01 0.15 0.13

Residual Solvent Analysis by GC/FID Headspace

FID1 A, (F-002-20-RME-006 FC12161904 10.28mg.D)	Column:	DB-ALC1 30 m	x 0.53 mm,
Norm 200 -		3 µm film thickı	ness
	Temp Program:	40°C hold 12 m	in to 220°C at
175-		40°C/min hold	5.5 min
	Carrier Gas:	Helium	
190 -	Flow Rate:	2.0 mL/min	
125 -	Detector Heater Temp:	250°C	
	Injector:	Headspace Sam	pler
100 -	HS Oven Temp:	60°C	
75-	Vial Equilibration:	10 minutes	
	Sample Name:	FC12161904	
75	Acquired:	March 04, 2020	
	Peak Compound	Area	Weight %
0-	1 NMP	NA	NA
0 2.5 5 7.5 10 12.5 15 17.5 20 mir	Total		ND
		ND- None Detec	cted



LC/MS



Isotopic Purity by LC/MS SIM

Certificate Page 9 of 10



Stability

Short term stability studies have been performed in multiple storage conditions for a period of up to four weeks. Short term data is utilized 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 stability findings for this product is listed below.

Storage Condition	Mean Kinetic Temperature (MKT)	Time Period/Result		
Freezer	-15°C			
Refrigerator	4°C	No decrease in purity was noted after		
Room Temperature	21°C	four weeks.		
40°C	40°C			
<i>Transport/Shipping:</i> Stability studies support the transport of this product at ambient conditions.				

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	June 05, 2020	Initial version.



Certified Reference Material - Certificate of Analysis

Н	ydrocodone, Primary Measurement Standard	Cerilliant Quality
	4,5-α-Epoxy-3-methoxy-17-methylmorphinan-6-one	ISO 17034
Product No.:	H-003-1ML	ISO/IEC 17025
Lot No.:	FE01082011	100/120 17020
Description of CRM	Hydrocodone in Methanol (Solution)	ISO 13485
Expiration Date:	January 2025 See Section "Stability Assessment".	ISO 14001
Storage:	Store unopened in freezer (-10 °C to -25 °C).	ISO 9001
Shipping:	Ambient. See Section "Stability Assessment".	
Chemical formula:	C ₁₈ H ₂₁ NO ₃	Ĺ
CAS No.:	125-29-1 0	<u> </u>
Regulatory:	USDEA Exempt Canadian TK # 61-1213	Ň CH ₃

Analyte		Certified Concentration \pm associated uncertainty U, $u=k*u$ (k=2)		
Hydrocodo	ne	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 characterized star page 2.	e is calculated from high precision weighing of thoroughly ting material. See "Details about certification process" on		
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 μ L for quantitative applications			
Instructions for handling and correct use: Health and safety information:	Concentration is corrected for chromatographic purity, residual water, 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. Danger. Please refer to the Safety Data Sheet for detailed information about the nature of any bazard and appropriate procautions to be taken.			
information:	the nature of any			
Accreditation:	Cerilliant Corp. is registered referent and registered tes	accredited by the US accreditation authority ANAB as acce material producer AR-1353 in accordance with ISO 17034 sting laboratory AT-1352 according to ISO/IEC 17025.		



Darron Ellsworth, Quality Assurance Manager

February 19, 2020

Issue Date

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 17034 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.



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 17034, 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 calculated 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 are analytically 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:	HPLC/UV	Calibration	Curve:	Linear Regression
Column:	Ascentis Express C18, 2.7 µm, 3.0 x 100 mm	Number of Points: 4		4
Mobile Phase:	Acetonitrile:0.1% Phosphoric acid in Water (12:88)	Linearity (r)):	1.000
Flow Rate:	1.8 mL/min			
Wavelength:	225 nm			
	Verified Concentration	n (mg/mL)	%F	RSD - Homogeneity

		Vernica concentration (mg/mz)	/oneb monogenency
Standard Solution	Lot Number	Actual Results	Actual Results
New Lot	FE01082011	1.004	0.2
Previous Lot	FE04241902	1.000	0.2

• 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: Material Lot:	Hydrocodone FC08241802	Chemical Form CAS Number: Molecular Weig	nula: C ₁₈ H ₂₁ NO ₃ 125-29-1 ght: 299.36			
Material Characterization Summary						
Analytical Test		Method	Results			
Primary Chromatographic Purity by HPLC/UV Analysis		SP10-0102	99.8%			
Secondary Chromatographic Purity by GC/FID Analysis		SP10-0101	99.5%			
Identity by LC/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	0.27%			
Residual Water Analysis by Karl Fischer Coulometry		AM1346 ¹	Not Detected			
Inorganic Content by Microash Analysis		SP10-0135	< 0.2%			
Mass Balance Purity Factor			99.53%			

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.
Spectral and Physical Data

HPLC/UV



Column:	Ascentis	Ascentis Express C18, 2.7 µm		
	3.0 x 10	3.0 x 100 mm		
Mobile Pha	se: A: Aceto	nitrile		
	B: 0.1%	Phosphori	c acid in	Water
Gradient:	Time (m	in) % A	% B	
	0.0	2	98	
	8.0	60	40	
	10.0	60	40	
	10.1	2	98	
Flow Rate:	0.6 mL/ı	nin		
Wavelengt	h: 225 nm			
	EC08241	902		
Sample Na	Me: FC06241	.002	0	
Acquirea:	Novemb	er 08, 201	8	
Peak #	Ret Time	Area %	•	
1	2.99	0.02		
2	3.74	99.80		
3	4.00	0.06		
4	4.08	0.09		

6.19

0.03

GC/FID



	Column: Temp Prog Injector To Detector T	DB-35 1.0 µr gram: 40°C 200°C hold 1 emp: Cool-0 remp: 325°C	DB-35ms, 30 m x 0.53 mm ID, 1.0 µm film thickness 40°C to 200°C at 40°C/min 200°C to 280°C at 5°C/min hold 18 min Cool-on-Column 325°C	
	Sample Na Acquired: Peak #	ame: FC082 Nover	241802 nber 13, 2018 Area %	
I	1	15.23	0.01	
I	2	15.77	0.02	
I	3	16.34	0.01	
-	4	17.42	0.35	
nir	5	17.94	99.51	
	6	18.36	0.02	
	7	18.78	0.04	
	8	19.27	0.03	

5

Residual Solvent Analysis by GC/FID Headspace



¹H NMR



LC/MS



Stability

Short term stability studies have been performed in multiple storage conditions for a period of up to four weeks. Short term data is utilized 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 stability findings for this product is listed below.

Storage Condition	Mean Kinetic Temperature (MKT)	Time Period/Result	
Freezer	-15°C		
Refrigerator	4°C	No decrease in purity was noted after	
Room Temperature	21°C	four weeks.	
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	February 19, 2020	Initial version.



Certified Reference Material - Certificate of Analysis

Hydrocodone-D ₆ , Primary Measurement Standard			Cerilliant Quality			
(5α) -4,5-Epoxy-3-trideuteromethoxy-17-trideuteromethylmorphinan-6-one		one	ISO 17034			
Product No.:		H-048-1ML			ISO/IEC 17025	
Lot No.:		FE01142004				ISO 13485
Description of (CRM:	Hydrocodone-	$_{6}$ in Methanol (Solution	on)		150 14001
Expiration Date:		January 2025	See Section	"Stability Assessment".		130 14001
Storage:		Store unopene	d in freezer (-10 °C to	o −25 °C).		ISO 9001
Shipping:		Ambient.	See Section "Stability	/ Assessment".		\sim
Chemical formu	ula:	$C_{18}H_{15}D_6NO_3$			°	
CAS No.:		1007844-38-3			0	Ĭ
Regulatory:		USDEA Exemp	Canadian TK # 61-	1228	0	N-CD3

Analyte		Certified Concentration \pm associated uncertainty U, u=k*u (k=2)
Hydrocodone	e-D ₆	1.000 ± 0.006 mg/mL
Metrological traceability:	y: 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 characterized star page 2.	e is calculated from high precision weighing of thoroughly ting material. See "Details about certification process" on
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 μ L for quantitative applications	
Instructions for handling and correct use:	Concentration is corrected for chromatographic purity, residual water, 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. For MS Applications, we advise laboratories not to mix lots during a single	
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 registered referen and registered tes	accredited by the US accreditation authority ANAB as accredited by the US accreditation authority ANAB as accerdance with ISO 17034 sting laboratory AT-1352 according to ISO/IEC 17025.



March 02, 2020

Darron Ellsworth, Quality Assurance Manager

Issue Date

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 17034 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.



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 17034, 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 calculated 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 are analytically 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:	HPLC/UV	Calibration Curve:	Linear Regression	
Column:	Ascentis Express C18, 2.7 µm, 3.0 x 100 mm	Number of Points:	4	
Mobile Phase:	Acetonitrile:0.1% Phosphoric acid in Water (15:85)	Linearity (r) :	1.000	
Flow Rate:	1.5 mL/min			
Wavelength:	225 nm			
	Varified Concentration	(mg/ml) 0/1	PSD - Homogonoity	

			%KSD - Holliogeneity	
Standard Solution	Lot Number	Actual Results	Actual Results	
New Lot	FE01142004	1.001	1.2	
Previous Lot	FE02081801	1.002	1.5	

 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: Material Lot:	Hydrocodone-D ₆ FC11301601	Chemical Form CAS Number: Molecular Weig	nula: C ₁₈ H 100 ght: 305	l ₁₅ D ₆ NO₃ 7844-38-3 .40
	Material Ch	aracterization Summary		
Analytical Test		Method	Res	ults
Primary Chromatographi Analysis	c Purity by HPLC/UV	SP10-0102	99.	7%
Secondary Chromatogra Analysis	phic Purity by GC/FID	SP10-0101	99.	7%
Identity by GC/MS Analysis		SP10-0105	Consistent w	ith Structure
Isotopic Purity and Distribution by GC/MS SIM Analysis		SP10-0105	0.01% D ₀ vs D ₆	
			0.01% D_0 to D_1	1.23% D ₄
			0.07% D ₂	12.61% D ₅
			0.17% D ₃	85.90% D ₆
Identity by ¹ H-NMR Analysis		USP <761>, SP10-0116	Consistent w	ith Structure
Residual Solvent Analysis by GC/FID Headspace		AM1087 ¹	0.41%	
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			99.2	28%

- 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.

Spectral and Physical Data

HPLC/UV



7.68

13

0.00

GC/FID



Column:	DB-5m 1.5 um	s, 30 m x 0.53 ı film thickness	mm ID,	
Temp Prog	ram: 40°C to 200°C	40°C to 200°C at 40°C/min 200°C to 280°C at 5°C/min hold 18 min		
Injector Te	mp: Cool-or	n-Column		
Detector Te	mp: 325°C			
Sample Nar Acquired:	me: FC1130 Februa	01601 ry 22, 2017		
Peak #	Ret Time	Area %		
1	13.99	0.08	-	
2	14.19	0.01		
3	15.44	0.00		
4	15.87	0.00		

99.68

0.01

0.00

0.02

0.02

0.11

0.00

0.01 0.03

0.02

5

6

7

8

9

10

11

12

13

14

16.25

16.52

16.72

16.93

17.17

17.64

18.92

19.82

21.26

27.49

Residual Solvent Analysis by GC/FID Headspace





Certificate Page 8 of 10

GC/MS



Cerilliant Corporation, 811 Paloma Drive, Suite A Round Rock, TX 78665, USA, Tel: 800-848-7837 / 512-238-9974

Stability

Short term stability studies have been performed in multiple storage conditions for a period of up to four weeks. Short term data is utilized 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 stability findings for a related product (H-008, Hydrocodone-D₃) is listed below.

Storage Condition	Mean Kinetic Temperature (MKT)	Time Period/Result	
Freezer	-15°C		
Refrigerator	4°C	No decrease in purity was noted after	
Room Temperature	21°C	four weeks.	
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	March 02, 2020	Initial version.



Certified Reference Material - Certificate of Analysis

He	Cerilliant Quality			
Morphinan-3,6-diol-7,8-didehydro-4,5-epoxy,17, methyl-(5α, 6α)-3,6-diacetate				
Product No.:	H-038-1ML	ISO/IEC 17025		
Lot No.:	FE01082016	150 12495		
Description of CRM:	Heroin in Acetonitrile (Solution)	130 13405		
Expiration Date:	January 2025 See Section "Stability Assessment".	ISO 14001		
Storage:	Store unopened in freezer (-10 °C to -25 °C).	ISO 9001		
Shipping:	Ambient. See Section "Stability Assessment". $H_3C_{\checkmark}O_{\checkmark}$	\land		
Chemical formula:	C ₂₁ H ₂₃ NO ₅			
CAS No.:	561-27-3			
Regulatory:	USDEA Exempt Canadian TK # 61-1225	N.CH3		

Analyte	Certified Concentration \pm associated uncertainty U, $u=k*u$ (k=2)			
Heroin	1.000 ± 0.006 mg/mL			
Metrological traceability: Traceable to the SI and higher order standards from NIST through an				

Metrological traceability.	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 μ L for quantitative applications
Instructions for handling and correct use:	Concentration is corrected for chromatographic purity, residual water, 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 17034 and registered testing laboratory AT-1352 according to ISO/IEC 17025.



Darron Ellsworth, Quality Assurance Manager

February 24, 2020

Issue Date

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 17034 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.



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 17034, 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 calculated 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 are analytically 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	Calibration C	Curve		
Analysis Method:	HPLC/UV	Calibration C	Curve:	Linear Regression
Column:	Ascentis Express C18, 2.7 µm, 3.0 x 100 mm	Number of P	oints:	4
Mobile Phase:	Acetonitrile:0.1% Phosphoric acid in Water (20:80)	Linearity (r)	:	1.000
Flow Rate:	1.2 mL/min			
Wavelength:	235 nm			
	Verified Concentration	n (mg/mL)	%F	RSD - Homogeneity

Standard Solution	Lot Number	Actual Results	Actual Results
New Lot	FE01082016	0.994	0.2
Previous Lot	FE06151603	1.000	0.4

• 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: Material Lot:	Heroin FC11111601	Chemical Form CAS Number: Molecular Weig	Dula: C ₂₁ H ₂₃ NO ₅ 561-27-3 ght: 369.41
	Material Characte	erization Summary	
Analytical Test		Method	Results
Primary Chromatographi	c Purity by HPLC/UV Analysis	SP10-0102	99.8% ¹
Secondary Chromatogra	ohic Purity by GC/FID Analysis	SP10-0101	99.8%
Identity by LC/MS Analysis		SP10-0107	Consistent with Structure
Identity by ¹ H-NMR Analysis		SP10-0116	Consistent with Structure
Residual Solvent Analysis by GC/FID Headspace		AM1087 ²	0.47%
Residual Water Analysis by Karl Fischer Coulometry		AM1346 ²	Not Detected
Inorganic Content by Microash Analysis		SP10-0135	< 0.2%
Mass Balance Purity Fact	or		99.37%

¹ No 6-Acetylmorphine or Morphine were detected by HPLC/UV analysis.

² 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.

Spectral and Physical Data

HPLC/UV



Column:	Ascentis Ex	press C	18, 2.7 µ	ım,
Mohilo Dhacau		rilo		
Mobile Phase:		nie Soonbori		Matan
• " ·	B: 0.1% Pr	iosphori	c acid in	water
Gradient:	Time (min)	% A	% B	
	0.0	2	98	
	8.0	50	50	
	10.0	50	50	
	10.1	2	98	
Flow Rate:	0.8 mL/mir	า		
Wavelength:	235 nm			
Sample Name:	FC1111160	1		
Acquired:	October 18	, 2019		
-		-		
Peak # Ret	Time	Area %		
1 3	3.40	0.02		
2 3	3.67	0.01		
3 4	1.32	0.06		
4 4	1.48	0.01		
5 4	1.64	0.01		
6 4	1.67	99.83		
7 4	1.99	0.02		
8 5	5.10	0.01		
9 5	5.22	0.01		

GC/FID



Column:		-5ms, 30 m x 0.53 mm ID, um film thickness		
Temp Program:		40°C to 200°C at 40°C/min		
		0°C to 280°C at 5°C/min		
	hol	d 18 min		
Injector To	emp: Co	ol-on-Column		
Detector Temp:		5°C		
Sample Na	me: FC	FC11111601		
Acquired:	No	vember 17, 2016		
Peak #	Ret Time	e Area %		
1	16.14	0.09		
2	16.34	0.02		
3	16.46	0.01		

17.86

18.79

23.53

6.99

0.01

99.84

0.03

0.01

4

5

6

10

Residual Solvent Analysis by GC/FID Headspace



¹H NMR





LC/MS

Column:	Ascentis Express C18, 2.7 µm,		Flow Rate:	0.4 mL/min	
	3.0 x 50 mm	า		Scan Range:	100-1200 amu
Mobile Phase:	A: 0.1% For	mic aci	d in Wate	Ionization:	Electrospray, Positive Ion
	B: Acetonitri	le		Instrument:	Waters XEVO G2 QTOF
Gradient:	Time (min)	% A	% B	Acquired:	October 21, 2019
	0.0	90	10		
	0.5	90	10		
	4.0	50	50		
	5.8	50	50		
	6.0	90	10		
	8.0	90	10		



Stability

Short term stability studies have been performed in multiple storage conditions for a period of up to four weeks. Short term data is utilized 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 stability findings for this product is listed below.

Storage Condition	Mean Kinetic Temperature (MKT)	Time Period/Result		
Freezer	-15°C			
Refrigerator	4°C	No decrease in purity was noted after		
Room Temperature	21°C	four weeks.		
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	February 24, 2020	Initial version.



Certified Reference Material - Certificate of Analysis

Heroin-D ₉ , Primary Measurement Standard					
7,8-Didehydro-4,5-epoxy-17-trideuteromethyl-morphinan-3,6-diol di[trideuteroacetate]					
Product No.:	H-037-1ML		ISO/IEC 17025		
Lot No.:	FE03022011		ISO 13485		
Description of CRM:	Heroin-D ₉ in	Acetonitrile (Solution)	ISO 14001		
Expiration Date:	April 2025	See Section "Stability Assessment".	ISO 9001		
Storage:	Store unopen	ed in freezer (-10 °C to -25 °C).			
Shipping:	Ambient.	See Section "Stability Assessment".			
Chemical formula:	$C_{21}H_{14}D_9NO_5$				
CAS No.:	1338713-49-	7			
Regulatory:	USDEA Exem	pt Canadian TK # 61-1224			

Analyte	Certified Concentration ± associated uncertainty U, u=k*u (k=2)		
Heroin-D ₉	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.

The certified value is calculated from high precision weighing of thoroughly Measurement method: 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. 1 µL for quantitative applications Minimum sample size: Concentration is corrected for chromatographic purity, residual water, residual Instructions for solvents, and residual inorganics. No adjustment required before use. handling and correct Users should quantitatively transfer desired volume using established good use: laboratory practices to spike into matrix or to dilute to the desired concentration. Each ampoule is intended for one-time use. For MS Applications, we advise laboratories not to mix lots during a single sequence. Health and safety Danger. Please refer to the Safety Data Sheet for detailed information about the nature of any hazard and appropriate precautions to be taken. information: Cerilliant Corp. is accredited by the US accreditation authority ANAB as Accreditation: registered reference material producer AR-1353 in accordance with ISO 17034 and registered testing laboratory AT-1352 according to ISO/IEC 17025.



Darron Ellsworth, Quality Assurance Manager

April 24, 2020

Issue Date

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 17034 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.



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 17034, 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 calculated 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 are analytically 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	Calibration Curve					
Analysis Method:	HPLC/UV		Calibration Curve:		Linear Regression	
Column:	: Ascentis Express C18, 2.7 µm, 3.0 x 100 mm			Number of Points: 4		
Mobile Phase:	Acetonitrile:0.1% Phosphoric acid in Water (20:80)			Linearity (r) : 1.000		
Flow Rate:	1.5 mL/min					
Wavelength:	Vavelength: 235 nm					
		Verified Concentration	(mg/mL)	%F	RSD - Homogeneity	
Standard						

Standard Solution	Lot Number	Actual Results	Actual Results	
New Lot	FE03022011	0.997	0.3	
Previous Lot	FE05251701	1.010	0.2	
Previous Lot	FE05251701	1.010	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.

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: Material Lot:	Heroin-D ₉ FC10151901	Chemical Form CAS Number: Molecular Wei	ula: C ₂₁ H ₁₄ D ₉ NO ₅ 1338713-49-7 Jht: 378.47		
	Material Charact	erization Summary			
Analytical Test		Method	Results		
Primary Chromatographic	c Purity by HPLC/UV Analysis	SP10-0102	99 .6% ¹		
Secondary Chromatograp	phic Purity by GC/FID Analysis	SP10-0101	99.	8%	
Identity by GC/MS Analy	sis	SP10-0105	Consistent w	ith Structure	
			0.02% D ₀ vs D ₉		
		SP10-0105	0.01% D_0 to D_1	0.42% D ₆	
Isotopic Purity and Distri	bution by GC/MS SIM Analysis		0.02% D ₂	5.22% D ₇	
			0.03% D ₃ to D ₄	17.09% D ₈	
			0.06% D ₅	77.11% D ₉	
Identity by ¹ H-NMR Analy	ysis	USP <761>, SP10-0116	Consistent w	ith Structure	
Residual Solvent Analysis by GC/FID Headspace		AM1087 ²	0.37%		
Residual Water Analysis	by Karl Fischer Coulometry	AM1346 ²	Below Quantitation Limit		
Inorganic Content by Mic	croash Analysis	SP10-0135	< 0.2%		
Mass Balance Purity Fact	or		99.2	28%	

¹ 0.07% 6-Acetylmorphine detected by HPLC/UV analysis.

² 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.

Spectral and Physical Data

HPLC/UV

Γ	DAD1 A, Sig=235,4 Ref=off (004-P2-A2-RNIH-003 FC10151901.D)	Column:	A	scentis Exp	oress C1	8, 2.7 µ	ım,
mAL			3	.0 x 100 m	m		
200		Mobile Phas	se: A	: Acetonitr	ile		
175	5-		В	: 0.1% Pho	osphoric	acid in	Water
		Gradient:	Ti	ime (min)	% A	% B	
150)-			0.0	2	98	
				8.0	50	50	
125	j-			10.0	50	50	
100				10.1	2	98	
100		Flow Rate:	0	.8 mL/min			
75	5-	Wavelength	i: 2	35 nm			
50	1-	Sample Nan	ne: F	C10151901			
		Acquired:	N	larch 05, 2	020		
25	− − − − − − − − − − − − − − − − − − −						
		Peak #	Ret lin	ne A	rea %		
		1	0.51		0.01		
	2 4 6 8 10 mir	2	3.44		0.07		
		3	4.58		99.67		
		4	4.82		0.08		
		5	4.89		0.03		
		6	4.95		0.01		
		/	5.20		0.04		
		8	5.25		0.07		
		9	5.33		0.03		

Peak 2 is identified as 6-Acetylmorphine



Residual Solvent Analysis by GC/FID Headspace



Column: Temp Pro	ogram:	DB-ALC1 30 m x 0.53 mm, 3 µm film thickness 40°C hold 12 min to 220°C at 40°C/min hold 5 5 min			
Carrier G	ias:	Helium			
Flow Rat	e:	2.0 mL/min			
Detector	Heater Temp:	250°C			
Injector:		Headspace Sampler			
HS Oven	Temp:	60°C			
Vial Equilibration:		10 minutes			
Sample I	Name:	FC10151901			
Acquired	:	March 04, 2020			
Peak	Compound	Area Weight %			
1	Dichloromethar	ne 27.52 0.35			
2	Ethyl acetate	4.80 0.02			
3	NMP	NA NA			
Total		0.37			



GC/MS



Stability

Short term stability studies have been performed in multiple storage conditions for a period of up to four weeks. Short term data is utilized 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 stability findings for this product is listed below.

Storage Condition Mean Kinetic Temperature (MKT)		Time Period/Result		
Freezer	-15°C			
Refrigerator	4°C	No decrease in purity was noted after four weeks.		
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	April 24, 2020	Initial version.



Certified Reference Material - Certificate of Analysis

(-)-L	evamisole, Prin	nary Measurement Sta	ndard	Cerilliant Quality
				ISO 17034
Product No.:	L-025-1ML			ISO/IEC 17025
Lot No.:	FN01142005			
Description of CRM:	(-)-Levamisole HC	l in Methanol (Solution)		ISO 13485
••••	Nominal concentra	ition is adjusted for HCl content.		ISO 14001
Expiration Date:	January 2025	See Section "Stability Assess	ment".	ISO 9001
Storage:	Store unopened in	freezer (-10 °C to -25 °C).		
Shipping:	Ambient. See	e Section "Stability Assessment".		HCI
Chemical formula:	$C_{11}H_{12}N_2S \bullet HCI$			
CAS No.:	16595-80-5			$\langle N = \langle N \rangle$

Analyte		Certified Concentration ± associated uncertainty U, u=k*u (k=2)
(-)-Levamisole		1.000 ± 0.006 mg/mL
Metrological traceability:	Traceable to the S unbroken chain of page 2.	SI and higher order standards from NIST through an f comparisons. See "Details on metrological traceability" on
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:	$1 \ \mu L$ for quantitat	ive applications
Instructions for handling and correct use:	Concentration is corrected for chromatographic purity, residual water, 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. Nominal concentration is adjusted for HCl content. No adjustment required before use.	
Health and safety information:	Danger. Please re the nature of any	fer to the Safety Data Sheet for detailed information about hazard and appropriate precautions to be taken.
Accreditation:	Cerilliant Corp. is registered referen and registered tes	accredited by the US accreditation authority ANAB as ince material producer AR-1353 in accordance with ISO 17034 sting laboratory AT-1352 according to ISO/IEC 17025.



Darron Ellsworth, Quality Assurance Manager

March 03, 2020

Issue Date

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 17034 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.



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 17034, 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 calculated 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 are analytically 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:	HPLC/UV	Calibration Curve:	Linear Regression
Column:	Ascentis Express Phenyl-Hexyl, 2.7 μm, 3.0 x 100 mm	Number of Points:	4
Mobile Phase:	Acetonitrile:0.1% Phosphoric acid in Water (15:85)	Linearity (r) :	1.000
Flow Rate:	1.3 mL/min		
Wavelength:	220 nm		
	Verified Concentration	n (mg/mL) %	RSD - Homogeneity

		Vernica concentration (mg/me)	/ittob monogeneity	
Standard Lot Number		Actual Results	Actual Results	
New Lot	FN01142005	0.997	0.7	
Previous Lot	FN08261801	0.999	0.6	

• 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 and salt adjustment are utilized to calculate the weighing adjustment necessary to ensure accuracy of the solution standard concentration.

Material Name: Material Lot: Chemical Formula: CAS Number:	(-)-Levamisole HCl PN030311-02 $C_{11}H_{12}N_2S \bullet$ HCl 16595-80-5	Molecular Weig Molecular Weig Salt Adjustmer	ght (base):204.29ght (salt):240.75nt:1.178	
	Material Characte	erization Summary		
Analytical Test		Method	Results	
Primary Chromatographic Purity by HPLC/UV Analysis		SP10-0102	> 99.9%	
Secondary Chromatographic Purity by GC/FID Analysis		SP10-0101	> 99.9%	
Identity by LC/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			99.98%	

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.

Spectral and Physical Data

HPLC/UV



GC/FID



Residual Solvent Analysis by GC/FID Headspace



¹H NMR

Instrument:	JEOL ECS 400
Solvent:	DMSO-D ₆



LC/MS

Column: Ascentis Express C18, 2.7 µm, 0.4 mL/min Flow Rate: 100-1200 amu 3.0 x 50 mm Scan Range: A: 0.1% Formic acid in Water Mobile Phase: Ionization: Electrospray, Positive Ion **B:** Acetonitrile Instrument: Waters XEVO G2 QTOF Gradient: Time (min) % A % B Acquired: June 18, 2018 0.0 90 10 0.5 90 10 4.0 50 50 5.8 50 50 6.0 90 10 8.0 90 10 (-)-Levamisole HCI Cone Voltage: 15.00000000 PRM-253 PN030311-02 W06181806 288 (1.105) Cm (283:291) 1: TOF MS ES+ 8.17e5 205.0793 100 Theoretical [M + H]+: 205.0799 Found [M + H]⁺: 205.0793 % 206.0823 178.0685 0---------- m/z πп 100 200 300 400 500 600 700 800 900 1000 1100

Stability

Short term stability studies have been performed in multiple storage conditions for a period of up to four weeks. Short term data is utilized 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 stability findings for this product is listed below.

Storage Condition	Mean Kinetic Temperature (MKT)	Time Period/Result			
Freezer	-15°C				
Refrigerator	4°C	No decrease in purity was noted after four weeks.			
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 57 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	March 03, 2020	Initial version.



Certified Reference Material - Certificate of Analysis

(-)-Levamisole-D₅, Primary Measurement Standard

(6S)-6-(2,3,4,5,6-Pentadeuteriophenyl)-2,3,5,6-tetrahydroimidazo[2,1-b][1,3]thiazole hydrochloride

Product No.:	L-058-1ML	ISO/IEC 17025
Lot No.:	FN03242016	ISO 13485
Description of CRM:	(-)-Levamisole-D ₅ HCI in Methanol (Solution)	ISO 14001
	Nominal concentration is adjusted for HCI content.	ISO 9001
Retest Date:	June 2021 See Section "Stability Assessment".	
Storage:	Store unopened in freezer (-10 °C to -25 °C).	
Shipping:	Ambient. See Section "Stability Assessment".	∕_N_∕
Chemical formula:	$C_{11}H_7D_5N_2S \cdot HCI$	N
CAS No.:	1246819-64-6 D D	

HCI

ISO 17034

Analyte		Certified Concentration ± associated uncertainty U, u=k*u (k=2)		
(-)-Levamisol	e-D ₅	1.000 ± 0.006 mg/mL		
Metrological traceability:	Traceable to the S chain of comparise	I and higher order standards from NIST through an unbroken ons. 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 quantitati	ve applications		
Instructions for handling and correct	Concentration is c solvents, and resid	orrected for chromatographic purity, residual water, residual dual inorganics. No adjustment required before use.		
use:	Users should quar laboratory practice concentration. Eac	ntitatively transfer desired volume using established good es to spike into matrix or to dilute to the desired ch ampoule is intended for one-time use.		
	Nominal concentration is adjusted for HCI content. No adjustment required before use.			
	For MS Applications, we advise laboratories not to mix lots during a single sequence.			
Health and safety information:Danger. Please ref nature of any hazaAccreditation:Cerilliant Corp. is registered reference and registered tes		fer to the Safety Data Sheet for detailed information about the ard and appropriate precautions to be taken.		
		accredited by the US accreditation authority ANAB as ce material producer AR-1353 in accordance with ISO 17034 ting laboratory AT-1352 according to ISO/IEC 17025.		



Darron Ellsworth, Quality Assurance Manager

May 02, 2020

Issue Date

Cerilliant Corporation, 811 Paloma Drive, Suite A Round Rock, TX 78665, USA, Tel: 800-848-7837 / 512-238-9974 L-058-1ML Revision 00

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 17034 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.



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 17034, 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 calculated 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

FN03242016

Solution New Lot

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		Calibration	Curve		
Analysis Method:	alysis Method: HPLC/UV		Calibration Curve: Linear Regre		Linear Regression
Column:	mn: Ascentis Express C18, 2.7 μm, 3.0 x 100 mm			Number of Points: 4	
Mobile Phase:	e: Acetonitrile: 0.1% Phosphoric acid in Water (12:88)		Linearity (r) : 1.000		1.000
Flow Rate:	1.7 mL/min				
Wavelength:	220 nm				
		Verified Concentration	(mg/mL)	%R	SD - Homogeneity
Standard	Lot Number	Actual Result	s		Actual Results

٠	Concentration is verified through multiple an	alyses and is calculated as the av	erage of multiple analyses compared
	to an independently prepared calibration solu	ition.	

1.002

 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.

0.5

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 and salt adjustment are utilized to calculate the weighing adjustment necessary to ensure accuracy of the solution standard concentration.

Material Name:	(-)-Levamisole-D ₅ HCl	Molecular Weig	ght (base):	209.32
Material Lot:	FN10151909	Molecular Wei	ght (salt):	245.78
Chemical Formula:	$C_{11}H_7D_5N_2S \bullet HCI$	Salt Adjustme	nt:	1.174
CAS Number:	1246819-64-6			
	Material Charact	erization Summary		
Analytical Test		Method	Res	ults
Primary Chromatographic	Purity by HPLC/UV Analysis	20384348	> 99	9.9%
Secondary Chromatograph	nic Purity by GC/FID Analysis	20384346	> 99	9.9%
Chiral Purity by HPLC/UV Analysis		20384348	69.2	% ee
Identity by LC/MS Analysis		20384217	Consistent with Structure	
			0.00% [D ₀ vs D ₅
Isotopic Purity and Distrib	ution by LC/MS SIM Analysis	20384217	0.00% D_0 to D_2	2.23% D ₄
			0.03% D ₃	97.73% D ₅
Identity by ¹ H-NMR Analys	sis	20384224	Consistent with Structure	
Residual Solvent Analysis by GC/FID Headspace		20397799 ¹	None Detected	
Residual Water Analysis by Karl Fischer Coulometry		20398075 ¹	Below Quantitation Limit	
Inorganic Content by Microash Analysis		20384350	< 0.2%	
Mass Balance Purity Facto	r		99.9	98%

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.

Spectral and Physical Data

HPLC/UV



GC/FID



Column: Temp Progra Injector Tem Detector Ter	DB-5 1.5 µ am: 40°C 140° np: Cool- np: 325°	ims, 30 m x 0.53 mm I Im film thickness to 140°C at 40°C/min C to 280°C at 5°C/min -on-Column C	D, hold 5 min
Sample Nam Acquired: Peak #	e: FN10 Marc Ret Time	0151909 h 24, 2020 Area %	
1	17.17	99.95	
2	19.15	0.01	
3	21.50	0.02	
4	22.31	0.01	

Spectral and Physical Data (cont.)



Chiral	Purity	Analysis	by HPLC/UV	
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Column: Mobile Ph Flow Rate Waveleng	C ase: H ({ :: 0 th: 2	hiral-Pak AD-H lexane:Ethanol: 80:20:0.5) .8 mL/min 35 nm	, 5 μm, 4.6 x 250 mm Diethylamine
Sample Na Acquired:	ame: F N	N10151909 Iarch 24, 2020	
Peak #	Ret Time	e Area %	
1	9.62	15.42	(+)-Levamisole-D ₅
2	11.91	84.58	(-)-Levamisole- D_5
	% ee = 69	9.16%	

Residual Solvent Analysis by GC/FID Headspace





LC/MS

Column: Ascentis Express C18, 2.7 µm, Flow Rate: 0.4 mL/min 3.0 x 50 mm 100-1200 amu Scan Range: Mobile Phase: A: 0.1% Formic acid in Water Ionization: Electrospray, Positive Ion **B:** Acetonitrile Instrument: Waters XEVO G2 QTOF Gradient: March 15, 2020 Time (min) % B Acquired: % A 0.0 98 2 0.5 2 98 70 4.0 30 5.8 70 30 6.0 98 2 8.0 98 2 RML-042 RML-042-S6B2H (-)-Levamisole-D5 HCI Cone Voltage: 20.0000000 W03152003 616 (2.315) 1: TOF MS ES+ 210.1120 6.66e5 100-Theoretical [M + H]+: 210.1113 Found [M + H]⁺: 210.1120 æ 211.1150 210.0752 0m/z 100 200 300 400 500 600 700 800 900 1000 1100

Isotopic Purity by LC/MS SIM



Stability

Short term stability studies have been performed in multiple storage conditions for a period of up to four weeks. Short term data is utilized 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 stability findings for a related product (L-025, (-)-Levamisole HCI) is listed below.

Storage Condition	Mean Kinetic Temperature (MKT)	Time Period/Result
Freezer	-15°C	
Refrigerator	4°C	No decrease in purity was noted aft
Room Temperature	21°C	four weeks.
40°C	40°C	
Transport/Shipping:	Stability studies support the transport of the transport of the stability studies support the transport of the stability studies are supported as the stability studies as the stabil	his product at ambient conditions.

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	May 02, 2020	Initial version.



Certified Reference Material - Certificate of Analysis

	Morphine, Primary Measurement Standard	Cerilliant Quality
	(5 α,6 α)-7,8-Didehydro-4,5-epoxy-17-methylmorphinan-3,6-diol	ISO 17034
Product No.:	M-005-1ML	ISO/IEC 17025
Lot No.:	FE01082017	150 13485
Description of CRM:	Morphine in Methanol (Solution)	130 13405
Expiration Date:	January 2025 See Section "Stability Assessment".	ISO 14001
Storage:	Store unopened in freezer (-10 °C to -25 °C).	ISO 9001
Shipping:	Ambient. See Section "Stability Assessment".	
Chemical formula:	C ₁₇ H ₁₉ NO ₃	
CAS No.:	57-27-2	
Regulatory:	USDEA Exempt Canadian TK # 61-1273	CH3

Analyte		Certified Concentration \pm associated uncertainty U, $u=k*u$ (k=2)
Morphine		1.000 ± 0.006 mg/mL
Metrological traceability:	Traceable to the S unbroken chain of page 2.	5I and higher order standards from NIST through an f comparisons. See "Details on metrological traceability" on
Measurement method:	The certified value characterized star page 2.	e is calculated from high precision weighing of thoroughly ting material. See "Details about certification process" on
Intended use:	This Certified Refe calibration, and q applications. Not	erence Material is suitable for the in vitro identification, uantification of the analyte(s) in analytical and R&D suitable for human or animal consumption.
Minimum sample size:	1 μ L for quantitat	ive applications
Instructions for handling and correct use: Health and safety	Concentration is of solvents, and resi Users should quar laboratory practic concentration. Ea Danger. Please re	corrected for chromatographic purity, residual water, residual dual inorganics. No adjustment required before use. ntitatively transfer desired volume using established good es to spike into matrix or to dilute to the desired ch ampoule is intended for one-time use. fer to the Safety Data Sheet for detailed information about
information:	the nature of any	nazard and appropriate precautions to be taken.
Accreditation:	Cerilliant Corp. is registered referent and registered tes	accredited by the US accreditation authority ANAB as the material producer AR-1353 in accordance with ISO 17034 sting laboratory AT-1352 according to ISO/IEC 17025.



Darron Ellsworth, Quality Assurance Manager

February 17, 2020

Issue Date

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 17034 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.



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 17034, 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 calculated 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 are analytically 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:	HPLC/UV	Calibration Curve:	Linear Regression
Column:	Ascentis Express Phenyl-Hexyl, 2.7 μm, 3.0 x 100 mm	Number of Points:	: 4
Mobile Phase:	Acetonitrile:0.1% Phosphoric acid in Water (8:92)	Linearity (r) :	0.997
Flow Rate:	1.5 mL/min		
Wavelength:	220 nm		
	Verified Concentration	n (mg/ml) °	%RSD - Homogeneity

		Vermed concentration (mg/me)	/orcsb = nonlogeneity
Standard Solution	Lot Number	Actual Results	Actual Results
New Lot	FE01082017	1.012	2.5
Previous Lot	FE08221801	1.010	2.8

• 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: Material Lot:	Morphine FC04091901	Chemical Form CAS Number: Molecular Weig	nula: C ₁₇ H ₁₉ NO ₃ 57-27-2 ght: 285.34
	Material Characte	erization Summary	
Analytical Test		Method	Results
Primary Chromatographi	ic Purity by HPLC/UV Analysis	SP10-0102	99.7%
Secondary Chromatogra	phic Purity by GC/FID Analysis	SP10-0101	99.8%
Identity by LC/MS Analy	sis	SP10-0107	Consistent with Structure
Identity by ¹ H-NMR Anal	lysis	USP <761>, SP10-0116	Consistent with Structure
Residual Solvent Analysi	s by GC/FID Headspace	AM1087 ¹	0.31%
Residual Water Analysis	by Karl Fischer Coulometry	AM1346 ¹	1.00%
Inorganic Content by Mi	croash Analysis	SP10-0135	< 0.2%
Mass Balance Purity Fac	tor		98.41%

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.

Spectral and Physical Data

HPLC/UV



Column:	Ascenti	is Express F	henyl-Hexy	ı,
	2.7 μm	, 3.0 x 100	mm	
Mobile Phas	se: A: Acet	tonitrile		
	B: 0.1º	% Phosphor	ic acid in W	ater
Gradient:	Time (r	nin) %A	% B	
	0.0	2	98	
	1.0	2	98	
	4.0	15	85	
	7.0	70	30	
	8.0	70	30	
	8.1	2	98	
Flow Rate:	0.7 mL	/min		
Wavelength	1: 220 nm	า		
Sample Nar	ne: FC0409	91901		
	1.1.00	2010		
Acquired:	July 09	, 2019		
Acquired: Peak #	July 09 Ret Time	, 2019 Area %	σ	
Acquired: Peak #	July 09 Ret Time 1.37	, 2019 Area % 0.06	<u>′o</u>	
Acquired: Peak # 1 2	July 09 Ret Time 1.37 1.83	, 2019 Area % 0.06 0.02	6	
Acquired: Peak # 1 2 3	July 09 Ret Time 1.37 1.83 1.95	Area 9 0.06 0.02 0.01	6	
Acquired: Peak # 1 2 3 4	July 09 Ret Time 1.37 1.83 1.95 2.68	Area 9 0.06 0.02 0.01 0.02	<u>'o</u>	
Acquired: Peak # 1 2 3 4 5	July 09 Ret Time 1.37 1.83 1.95 2.68 3.14	, 2019 Area 9 0.06 0.02 0.01 0.02 99.70	<u>6</u>	
Acquired: Peak # 1 2 3 4 5 6	July 09 Ret Time 1.37 1.83 1.95 2.68 3.14 3.51	, 2019 Area 9 0.06 0.02 0.01 0.02 99.70 0.07	<u>6</u>	
Acquired: Peak # 1 2 3 4 5 6 7	July 09 Ret Time 1.37 1.83 1.95 2.68 3.14 3.51 3.89	, 2019 Area 9 0.06 0.02 0.01 0.02 99.70 0.07 0.01	<u>6</u>	
Acquired: Peak # 1 2 3 4 5 6 7 8	July 09 Ret Time 1.37 1.83 1.95 2.68 3.14 3.51 3.89 3.91	Area 9 0.06 0.02 0.01 0.02 99.70 0.07 0.01 0.01	<u>6</u>	
Acquired: Peak # 1 2 3 4 5 6 7 8 9	July 09 Ret Time 1.37 1.83 1.95 2.68 3.14 3.51 3.89 3.91 4.26	Area 9 0.06 0.02 0.01 0.02 99.70 0.07 0.01 0.01 0.01 0.01	6	
Acquired: Peak # 1 2 3 4 5 6 7 8 9 10	July 09 Ret Time 1.37 1.83 1.95 2.68 3.14 3.51 3.89 3.91 4.26 4.77	Area 9 0.06 0.02 0.01 0.02 99.70 0.07 0.01 0.01 0.01 0.01 0.02	<u>6</u>	
Acquired: Peak # 1 2 3 4 5 6 7 8 9 10 11	July 09 Ret Time 1.37 1.83 1.95 2.68 3.14 3.51 3.89 3.91 4.26 4.77 5.05	Area 9 0.06 0.02 0.01 0.02 99.70 0.07 0.01 0.01 0.01 0.02 0.06	<u>6</u>	

GC/FID



Column:	DB-35m 1.0 µm	DB-35ms, 30 m x 0.53 mm ID, 1.0 μ m film thickness		
Temp Prog	ram: 40°C to 200°C t	40°C to 200°C at 40°C/min 200°C to 300°C at 5°C/min		
	hold 16	min		
Injector Te	mp: Cool-on	-Column		
Detector Te	emp: 325°C			
Sample Na	me: FC0409	1901		
Acquired:	July 13,	2019		
Peak #	Ret Time	Area %		
1	16.43	0.02		
2	17.29	0.09		
3	18.39	99.84		
4	19.68	0.03		
5	20.19	0.01		
6	21.19	0.01		

Residual Solvent Analysis by GC/FID Headspace

FID1 A, Front Signal (F-002-30-RMM-435 FC04091901 8.50mg D)	Column:	DB-ALC1 30 m x 0.53 mm, 3 um film thickness
100 -	Temp Program:	40°C hold 12 min to 220°C at 40°C/min hold 5.5 min
	Carrier Gas:	Helium
600 -	Flow Rate:	2.0 mL/min
	Detector Heater Temp	: 250°C
500	Injector:	Headspace Sampler
	HS Oven Temp:	60°C
400	Vial Equilibration:	10 minutes
300-	Sample Name:	FC04091901
200- 5	Acquired:	July 09, 2019
dettan.	Peak Compound	Area Weight %
	1 Methanol	33.99 0.31
	2 NMP	NA NA
	Total	0.31



LC/MS

Column:	Ascentis E	xpress C1	8, 2.7	μm,		Flow R Scan R	ate:	0.4 mL/min 100-1200 amu	
Mobile Phase:	A: 0.1% F B: Acetoni	ormic acio trile	d in Wa	iter		Ionizat Instrur	ion: nent:	Electrospray, Positive Ior Waters XEVO G2 QTOF	n
Gradient:	<u>Time (min</u> 0.0 0.5 4.0 5.8 6.0 8.0) % A 98 98 40 40 98 98	% B 2 60 60 2 2 2	-		Acquire	ed:	July 16, 2019	
RMM-035 FC04091901				Morphi	ne			Cone Voltage: 15.000000)(
W07161929 400 (1.505) Cm	<mark>(400:403)</mark> 286.1440	Theoretic Found [M	al [M ⊣ + H]+	- H]+: 286.14 : 286.1440	443			1: TOF MS ES- 2.05e	+ 36
158.9615	287.1472 288.1500			571.2798593.2640				m/	/7
100 200	300	400	500	600	700	800	900	1000 1100	-

Stability

Short term stability studies have been performed in multiple storage conditions for a period of up to four weeks. Short term data is utilized 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 stability findings for this product is listed below.

Storage Condition	Mean Kinetic Temperature (MKT)	Time Period/Result				
Freezer	-15°C					
Refrigerator	4°C	No decrease in purity was noted after				
Room Temperature	21°C	four weeks.				
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	February 17, 2020	Initial version.



Certified Reference Material - Certificate of Analysis

Morphine-D₆, Primary Measurement Standard

5a, 6a-7, 8-Didehydro-4, 5-epoxy-17-trideuteromethyl-15, 15, 16-trideutoeromorphinan-3, 6-diol

Product No.:	M-086-1ML				Cerilliant Quality
Lot No.:	FE02212001				ISO 17034
Description of CRM:	Morphine-D ₆ i	n Methanol (Solution)			ISO/IEC 17025
Expiration Date:	March 2025	See Section "St	tability Asse	ssment".	130/IEC 17025
Storage:	Store unopene	ed in freezer (-10 °C to -25 °C	C).		ISO 13485
Shipping:	Ambient.	See Section "Stability Asses	sment".	110	ISO 14001
Chemical formula:	$C_{17}H_{13}D_6NO_3$			HO D	ISO 9001
CAS No.:	1334606-17-5				
Regulatory:	USDEA Exemp	t Canadian TK # 61-1319		HO"	D ₃

Analyte	Certified Concentration \pm associated uncertainty U, u=k*u (k=2)
Morphine-D ₆	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 water, 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. For MS Applications, we advise laboratories not to mix lots during a single sequence.
Health and safety	Danger. Please refer to the Safety Data Sheet for detailed information about the

information: Accreditation:

Accreditation:

nature of any hazard and appropriate precautions to be taken. Cerilliant Corp. is accredited by the US accreditation authority ANAB as registered reference material producer AR-1353 in accordance with ISO 17034 and registered testing laboratory AT-1352 according to ISO/IEC 17025.



Darron Ellsworth, Quality Assurance Manager

July 31, 2020

Issue Date

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 17034 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.



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 17034, 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 calculated 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 are analytically 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.

Analysis Method:HPLC/UVCalibration Curve:Linear RegressionColumn:Ascentis Express Phenyl-Hexyl, 2.7 μm, 3.0 x 100 mmNumber of Points:4Mobile Phase:Acetonitrile:0.1% Phosphoric acid in Water (5:95)Linearity (r) :1.000Flow Rate:1.5 mL/min210 nmLinearity (r) :1.000	Standard Solution Assay Parameters			Calibration Curve		
Column:Ascentis Express Phenyl-Hexyl, 2.7 μm, 3.0 x 100 mmNumber of Points:4Mobile Phase:Acetonitrile:0.1% Phosphoric acid in Water (5:95)Linearity (r):1.000Flow Rate:1.5 mL/min210 nmLinearity (r):1.000	Analysis Method:	HPLC/UV		Calibration Cur	ve: Linea	ar Regression
Mobile Phase:Acetonitrile:0.1% Phosphoric acid in Water (5:95)Linearity (r):1.000Flow Rate:1.5 mL/min210 nm	Column:	Ascentis Express Pher 2.7 µm, 3.0 x 100 mr	ıyl-Hexyl, n	Number of Poir	1ts: 4	
Flow Rate:1.5 mL/minWavelength:210 nm	Mobile Phase:	Acetonitrile:0.1% Phc (5:95)	osphoric acid in Water	Linearity (r) :	1.00	0
Wavelength: 210 nm	Flow Rate:	1.5 mL/min				
	Wavelength:	210 nm				

		Verified Concentration (mg/mL)	%RSD - Homogeneity
Standard Solution	Lot Number	Actual Results	Actual Results
New Lot	FE02212001	1.000	0.8
Previous Lot	FE05121902	0.999	0.7

• 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.

Isotopic Distribution Comparison

The Previous Lot and the New Lot have different isotopic distributions (see table below). The analyzed concentration of the Previous Lot was adjusted for the % of D_6 relative to the New Lot. In MS applications, the New Lot can be expected to have a lower response than the Previous Lot when monitoring the D_6 mass/charge ratio.

Isotopic Distributi (Lot FE02	on of the New Lot 212001)	Isotopic Distribution of (Lot FE051	of the Previous Lot 21902)
%D ₀	0.00	%D ₀	0.00
%D ₁	0.01	%D ₁	0.01
%D ₂	0.26	%D ₂	0.04
%D ₃	4.61	%D ₃	1.17
%D ₄	13.89	%D ₄	1.54
%D ₅	8.81	%D ₅	8.88
%D ₆	70.77	%D ₆	86.57
%D ₇	1.58	%D ₇	1.68
%D ₈	0.07	%D ₈	0.12
%D ₀ vs D ₆	0.00	$%D_0$ vs D_6	0.00

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: Material Lot:	Morphine-D ₆ FC07311901	Chemical Form CAS Number: Molecular Weig	iula: C ₁₇ H ₁₃ D ₆ NO ₃ 1334606-17-5 ght: 291.37		
	Material Character	ization Summary			
Analytical Test		Method	Results		
Primary Chromatograph	ic Purity by HPLC/UV Analysis	20384348	99.3% ¹		
Secondary Chromatographic Purity by GC/FID Analysis		20384346	> 99.9%		
Identity by LC/MS Analysis		20384217	Consistent with Structure		
			0.00% D ₀ vs D ₆		
			0.00% D ₀	8.81% D ₅	
	·····	2020/217	0.01% D ₁	70.77% D ₆	
Isotopic Purity and Distr	ptopic Purity and Distribution by LC/MS SIM Analysis ² 20384217			1.58% D ₇	
			4.61% D ₃	0.07% D ₈	
			13.89% D ₄		
Identity by ¹ H-NMR Ana	lysis	20384224	Consistent with Structure		
Residual Solvent Analys	is by GC/FID Headspace	20397799 ³	1.33%		
Residual Water Analysis	by Karl Fischer Coulometry	20398075 ³	Below Quantitation Limit		
Inorganic Content by Mi	croash Analysis	20384350	< 0.2%		
Mass Balance Purity Fac	tor		97.96%		

¹ 0.01% 6-Acetylmorphine detected by HPLC/UV analysis

- 2 Isotopic distribution values are adjusted for the natural abundance of isotopes (M + 1 adjusted 19.03%; M + 2 adjusted 2.33%).
- ³ 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.

Spectral and Physical Data

HPLC/UV



Column:	Ascentis	Ascentis Express Phenyl-Hexyl,			
	2.7 µm,	2.7 μm, 3.0 x 100 mm			
Mobile Phase	e: A: Aceto	A: Acetonitrile			
	B: 0.1%	Phosphoric a	acid in W	ater	
Gradient:	Time (m	in) % A	<u>% B</u>		
	0.0	2	98		
	1.0	2	98		
	4.0	10	90 F0		
	7.0	50	50		
	9.0	50	08		
Flow Pater	9.1 0.8 ml/r	2 min	90		
Wavelength	210 nm				
wavelength.	210 1111				
Sample Nam	e: FC07311	.901			
Acquired:	January	30, 2020			
Peak # R	et Time	∆rea %			
1	0.95	0.01			
2	1.30	0.10			
3	1.55	0.07			
4	1.79	0.03			
5	1.90	0.09			
6	2.16	99.24			
7	2.63	0.12			
8	2.91	0.02			
9	3.16	0.04			
10	3.43	0.03			
11	3.54	0.02			
12	3.61	0.01			
13	3.76	0.00			
14	3.92	0.00			
15	4.58	0.07			
10	4.74	0.01			
18	5 32	0.01			
19	5 44	0.00			
20	5.59	0.01			
21	5.67	0.01			
22	5.79	0.00			
23	5.99	0.00			
24	6.17	0.04			
25	6.50	0.01			
26	6.53	0.01			
27	6.64	0.01			
28	6.69	0.00			
29	6.74	0.01			
30	7.76	0.01			

Peak #21 has been identified as 6-Acetylmorphine.



Column:DB-35ms, 30 m x 0.53 mm ID,
1.0 μm film thicknessTemp Program:40°C to 200°C at 40°C/min
200°C to 280°C at 5°C/min
hold 18 minInjector Temp:Cool-on-ColumnDetector Temp:325°C

 Sample Name:
 FC07311901

 Acquired:
 January 23, 2020

Peak	Ret Time	Area %
1	8.54	0.01
2	11.23	99.98
3	11.86	0.01
4	16.67	0.01

Residual Solvent Analysis by GC/FID Headspace



Columr	1:	DB-ALC1 30 m 3 um film thick	x 0.53 mm, ness	
Temp P	Program:	40°C hold 12 min to 220°C at		
-	-	40°C/min hold 5.5 min		
Carrier	Gas:	Helium		
Flow Ra	ate:	2.0 mL/min		
Detecto	or Heater Temp	: 250°C		
Injecto	r:	Headspace Sampler		
HS Ove	n Temp:	60°C		
Vial Eq	uilibration:	10 minutes		
Sample	Name:	FC07311901		
Acquire	ed:	January 07, 20	20	
Peak	Compound	Area	Weight %	
1	Methanol	116.52	1.22	
2	Ethanol	9.73	0.11	
3	NMP	NA	NA	

Total

1.33



LC/MS

ss C18, 2.7 μm, Flow Rate: 0.4 mL/min	s C18, 2	centis Expre	Asce	mn:	Colu
ic acid in Water Scan Range: 100-1200 amu Ionization: Electrospray, Positive Ion Instrument: Waters XEVO G2 OTOE	.0 x 50 mm x: 0.1% Formic acid in Water			Mobile Phase:	
% A % B Acquired: January 14, 2020	A %	me (min)	Tim	lient:	Grad
<u>98 2</u>	8	0.0			
98 2	8	0.5			
70 30	0 3	4.0			
70 30	'0 E	5.8			
98 2	8	6.0			
98 2	8	8.0			
Morphine-D6 Cone Voltage: 20.0000000			1901	1-039 FC0731	RMM
1: TOF MS ES+		403:407)	22) Cm (40	142028 405 (1.5)	W011
1.76e6		1817	292.18		400
					100-
pretical [M + H]+: 292.1820	etical [N	Theo			-
ud [M + H]+: 292.1817	- [M + F	Four			-
	[-
					-
					~
					-
		293.1852	290,1692 29		-
		/	Y		-
605 2201		314.1640	89,1636	2	_
ا ج/m ا حمد				141.9587	0_
) 500 600 700 800 900 1000 1100	5(00 40	30)0 200	
Pretical [M + H]+: 292.1820 Id [M + H]+: 292.1817 605.3391 0 500 600 700 800 900 1000 1100	etical [N [M + H	1817 Theo Four 293.1852 314.1640 	292.18 290.1692 29 89.1636 30	141.9587 ²	100
Isotopic Purity by LC/MS SIM



Cerilliant Corporation, 811 Paloma Drive, Suite A Round Rock, 1 TX 78665, USA, Tel: 800-848-7837 / 512-238-9974

Certificate Page 10 of 11

Stability

Short term stability studies have been performed in multiple storage conditions for a period of up to four weeks. Short term data is utilized 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 stability findings for a related product (M-109, Morphine) is listed below.

Storage Condition	Mean Kinetic Temperature (MKT)	Time Period/Result	
Freezer	-15°C		
Refrigerator	4°C	No decrease in purity was noted after four weeks.	
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	April 08, 2020	Initial version.
01	June 23, 2020	Added Isotopic Distribution Comparison table.
02	July 31, 2020	Corrected Isotopic Distribution Comparison to state "lower response".



Certified Reference Material - Certificate of Analysis

(±)-Methadone, Primary Measurement Standard		
	(±)-6-Dimethylamino-4,4-diphenyl-3-heptanone	ISO 17034
Product No.:	M-007-1ML	ISO/IEC 17025
Lot No.:	FE02272002	ISO 13485
Description of CRM:	(±)-Methadone in Methanol (Solution)	150 14001
Expiration Date:	March 2025 See Section "Stability Assessment".	130 14001
Storage:	Store unopened in freezer (-10 °C to -25 °C).	ISO 9001
Shipping:	Ambient. See Section "Stability Assessment".	
Chemical formula:	C ₂₁ H ₂₇ NO 0,	Сп ₃
CAS No.:	76-99-3	N N
Regulatory:	USDEA Exempt Canadian TK # 61-1275	CH ₃

Analyte		Certified Concentration \pm associated uncertainty U, u=k*u (k=2)
(±)-Methado	one	1.000 ± 0.006 mg/mL
Metrological traceability:	y: 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 μ L for quantitative applications	
Instructions for handling and correct use: Health and safety information:	Concentration is corrected for chromatographic purity, residual water, 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. 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 17034 and registered testing laboratory AT-1352 according to ISO/IEC 17025.	



Darron Ellsworth, Quality Assurance Manager

April 06, 2020

Issue Date

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 17034 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.



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 17034, 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 calculated 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 are analytically 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.

Assay Parameters	Calibration Curve	
GC/FID	Calibration Curve:	Linear Regression
DB-5ms 30 m x 0.53 mm ID, 1.5 µm film thickness	Number of Points:	4
60°C to 280°C at 40°C/min hold 7 min	Linearity (r) :	1.000
Cool-on-Column	_	
325°C		
	Assay Parameters GC/FID DB-5ms 30 m x 0.53 mm ID, 1.5 μm film thickness 60°C to 280°C at 40°C/min hold 7 min Cool-on-Column 325°C	Assay ParametersCalibration CurveGC/FIDCalibration Curve:DB-5ms 30 m x 0.53 mm ID,Number of Points:1.5 µm film thicknessNumber of Points:60°C to 280°C at 40°C/min hold 7 minLinearity (r) :Cool-on-Column325°C

		verified Concentration (mg/mL)	%RSD - Homogeneity
Standard Solution	Lot Number	Actual Results	Actual Results
New Lot	FE02272002	0.995	0.3
Previous Lot	FE08091801	0.993	0.5

• 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: Material Lot:	(±)-Methadone FC08301902	Chemical Form CAS Number: Molecular Weig	ula: C ₂₁ H ₂₇ NO 76-99-3 ght: 309.45
	Material Characte	erization Summary	
Analytical Test		Method	Results
Primary Chromatographic Purity by GC/FID Analysis		20384346	99.7%
Secondary Chromatographic Purity by HPLC/UV Analysis		20384348	> 99.9%
Identity by GC/MS Analysis		20384214	Consistent with Structure
Identity by ¹ H-NMR Analysis		20384224	Consistent with Structure
Residual Solvent Analysis by GC/FID Headspace		20397799 ¹	0.05%
Residual Water Analysis by Karl Fischer Coulometry		20398075 ¹	Below Quantitation Limit
Inorganic Content by Microash Analysis		20384350	< 0.2%
Mass Balance Purity Factor			99.69%

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.

Spectral and Physical Data

GC/FID



HPLC/UV

DAD1 A, Sig=214,4 Ref=off (004-P1-B2-RMM-044 FC08301902.D)	Column:	Ascentis Ex	press C1	8, 2.7 µm,
mAU : 20 400		3.0 x 50 mr	n	
	Mobile Phase:	A: Acetonitr	ile	
350 -		B: 0.1% Ph	osphoric	acid in Water
	Gradient:	Time (min)	% A	% B
300-		0.0	20	80
		5.0	80	20
250-		6.0	80	20
		6.1	20	80
200-	Flow Rate:	0.8 mL/min		
150-	Wavelength:	214 nm		
100-	Sample Name:	FC08301902	2	
	Acquired:	January 03,	2020	
50-				
2.03	Peak # Ret	Time A	rea %	
	1 2.	21	0.01	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	2 2	57	99.96	
	3 2.	.93	0.03	

Residual Solvent Analysis by GC/FID Headspace





GC/MS

Column:	DB-5ms 30 m x 0.25 mm ID,	Scan Range:	50-500 amu
Temp Program:	50°C to 200°C at 40°C/min 200°C to 300°C at 10°C/min hold 16 min	Acquired:	January 09, 2020
Abundance	Scan 376 (8.863 min): Z	01092007.D\data.ms	
8000000	72.2		
7000000			
6000000			
5000000			
4000000			
3000000			
2000000	91.1 165.1		
1000000 57.1	115.1	223.1	294.1
0	\cdot	236.2 250.2 265.1 28	0.1 309.3 341.0 355.1
m/z> 40 50 60	70 80 90 100 110 120 130 140 150 160 170 180 190 200 7	210 220 230 240 250 260 270 2	80 290 300 310 320 330 340 350 360

Stability

Short term stability studies have been performed in multiple storage conditions for a period of up to four weeks. Short term data is utilized 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 stability findings for a related product (M-008, (\pm) -Methadone-D₃) is listed below.

Storage Condition	Mean Kinetic Temperature (MKT)	Time Period/Result	
Freezer	-15°C		
Refrigerator	4°C	No decrease in purity was noted after four weeks.	
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	April 06, 2020	Initial version.



Certified Reference Material - Certificate of Analysis

(±)-Methadone-D ₉ , Primary Measurement Standard				
(±)-6-Di(trideu	teromethyl)amii	no-4,4-diphenyl-1-1-1,1-trideuteromethyl-3-heptanone	ISO 17034	
Product No.:	M-089-1ML		ISO/IEC 17025	
Lot No.:	FE01082012		ISO 13485	
Description of CRM:	(±)-Methadon	ne-D ₉ in Methanol (Solution)	100 1 4001	
Expiration Date:	January 2025	See Section "Stability Assessment".	150 14001	
Storage:	Store unopene	ed in freezer (-10 °C to -25 °C).	ISO 9001	
Shipping:	Ambient.	See Section "Stability Assessment".		
Chemical formula:	$C_{21}H_{18}D_9NO$		3	
CAS No.:	1435933-74-6	6 N N	·	
Regulatory:	USDEA Exemp	pt Canadian TK # 61-1321		

Analyte	Certified Concentration ± associated uncertainty U, u=k*u (k=2)
(±)-Methadone-D ₉	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 μ L for quantitative applications
Instructions for handling and correct use:	Concentration is corrected for chromatographic purity, residual water, 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. For MS Applications, we advise laboratories not to mix lots during a single sequence.
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 17034 and registered testing laboratory AT-1352 according to ISO/IEC 17025.



Darron Ellsworth, Quality Assurance Manager

February 18, 2020

Issue Date

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 17034 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.



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 17034, 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 calculated 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 are analytically 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
Temp Program:	60°C to 280°C at 40°C/min hold 7 min	Linearity (r) :	1.000
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	FE01082012	0.992	0.4	
Previous Lot	FE05101801	0.985	0.6	

• 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: Material Lot:	(±)-Methadone-D ₉ FC07311801	Chemical Form CAS Number: Molecular Weig	nula: C ₂₁ H 143 ght: 318	I ₁₈ D9NO 5933-74-6 .50
	Material Character	ization Summary		
Analytical Test		Method	Res	sults
Primary Chromatograph	ic Purity by GC/FID Analysis	SP10-0101	99.8%	
Secondary Chromatogra	phic Purity by HPLC/UV Analysis	SP10-0102	> 99	9.9%
Identity by GC/MS Analy	/sis	SP10-0105	Consistent v	vith Structure
			0.06% D ₀ vs D ₉	
		SP10-0105	0.05% D ₀	0.41% D ₅
	bution by GC/MS SIM Analysis		0.07% D ₁	1.23% D ₆
Isotopic Purity and Distr			0.13% D ₂	2.66% D ₇
			0.18% D ₃	12.40% D ₈
			0.50% D ₄	82.38% D ₉
			0.00%	D ₀ vs D ₉
Isotopic Purity and Distr	ibution by LC/MS SIM Analysis	SP10-0107	0.00% D_0 to D_7	98.31% D ₉
			1.69% D ₈	
Identity by ¹ H-NMR Analysis		USP <761>, SP10-0116	Consistent with Structure	
Residual Solvent Analysis by GC/FID Headspace		AM1087 ¹	0.02%	
Residual Water Analysis by Karl Fischer Coulometry		AM1346 ¹	None Detected	
Inorganic Content by Microash Analysis		SP10-0135	< 0.2%	
Mass Balance Purity Fac	tor		99.	75%

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.

Spectral and Physical Data

GC/FID



Column:DB-5ms, 30 m x 0.53 mm ID,
1.5 μm film thicknessTemp Program:40°C to 180°C at 40°C/min
180°C to 280°C at 5°C/min
hold 12 minInjector Temp:Cool-on-Column
325°C

 Sample Name:
 FC07311801

 Acquired:
 September 05, 2018

Peak #	Ret Time	Area %
1	9.42	0.00
2	10.09	0.01
3	12.02	0.02
4	12.69	0.02
5	12.82	0.00
6	13.51	99.81
7	14.23	0.02
8	14.37	0.02
9	14.90	0.04
10	15.25	0.06

HPLC/UV



Column:	Ascentis E	Ascentis Express C18, 2.7 µm,		
	3.0 x 50 r	nm		
Mobile Phase	A: Aceton	itrile		
	B: 0.1% F	Phosphoric	c acid in	Water
Gradient:	Time (min) % A	% B	
	0.0	20	80	
	5.0	80	20	
	6.0	80	20	
	6.1	20	80	
Flow Rate:	0.8 mL/m	in		
Wavelength:	214 nm			
Sample Name	e: FC073118	01		
Acquired:	August 30	, 2018		
Peak # Re	t Time	Area %		
1	2.54	99.98		
2	3.31	0.02		

Residual Solvent Analysis by GC/FID Headspace



¹H NMR



JEOL ECS 400

Instrument:

Isotopic Purity by LC/MS SIM



Certificate Page 8 of 10

Cerilliant Corporation, 811 Paloma Drive, Suite A Round Rock, TX 78665, USA, Tel: 800-848-7837 / 512-238-9974

GC/MS



Cerilliant Corporation, 811 Paloma Drive, Suite A Round Rock, TX 78665, USA, Tel: 800-848-7837 / 512-238-9974

Stability

Short term stability studies have been performed in multiple storage conditions for a period of up to four weeks. Short term data is utilized 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 stability findings for a related product (M-019, (±)-Methadone) is listed below.

Storage Condition	Mean Kinetic Temperature (MKT)	Time Period/Result	
Freezer	-15°C		
Refrigerator	4°C	No decrease in purity was noted after	
Room Temperature	21°C	four weeks.	
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	February 18, 2020	Initial version.



Certified Reference Material - Certificate of Analysis

(±)-Methamphetamine, Primary Measurement Standard

	1-Phenyl-2-methylaminopropane	Cerilliant Quality
Product No.:	M-009-1ML	ISO 17034
Lot No.:	FE03022006	ISO/IEC 17025
Description of CRM:	(±)-Methamphetamine in Methanol (Solution)	130/120 17023
Expiration Date:	March 2025 See Section "Stability Assessment".	ISO 13485
Storage:	Store unopened in freezer (-10 °C to -25 °C).	ISO 14001
Shipping:	Ambient. See Section "Stability Assessment".	ISO 9001
Chemical formula:	C ₁₀ H ₁₅ N H	
CAS No.:	7632-10-2	CH
Regulatory:	USDEA Exempt Canadian TK # 61-1277	

Analyte		Certified Concentration \pm associated uncertainty U, $u=k*u$ (k=2)
(±)-Methamphe	tamine	1.000 ± 0.006 mg/mL
Metrological traceability:	Traceable to the S unbroken chain o page 2.	SI and higher order standards from NIST through an f comparisons. See "Details on metrological traceability" on
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:	$1 \ \mu L$ for quantitat	ive applications
Instructions for handling and correct use: Health and safety information:	Concentration is of solvents, and residusers should quar laboratory practic concentration. Ea Danger. Please residue nature of any	corrected for chromatographic purity, residual water, residual idual inorganics. No adjustment required before use. Initiatively transfer desired volume using established good tes to spike into matrix or to dilute to the desired ch ampoule is intended for one-time use. Ifer to the Safety Data Sheet for detailed information about hazard and appropriate precautions to be taken.
Accreditation:	Cerilliant Corp. is registered referer and registered te	accredited by the US accreditation authority ANAB as nce material producer AR-1353 in accordance with ISO 17034 sting laboratory AT-1352 according to ISO/IEC 17025.



Darron Ellsworth, Quality Assurance Manager

July 16, 2020

Issue Date

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 17034 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.



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 17034, 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 calculated 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 are analytically 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.

	Assay Parameters	Calibration Curve	
Analysis Method:	GC/FID	Calibration Curve:	Linear Regression
Column:	DB-5ms 30 m x 0.53 mm ID, 1.5 μ m film thickness	Number of Points:	4
Injector Temp:	Cool-on-Column		1.000
Detector Temp:	325°C		

		Verified Concentration (mg/mL)	%RSD - Homogeneity	
Standard Lot Number		Actual Results	Actual Results	
Solution	Lot Number	Actual Results	Actual Results	
New Lot	FE03022006	1.015	0.6	
Previous Lot	FE01152002	1.018	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.

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: Material Lot:	(±)-Methamphetamine FC12131901	Chemical Formu CAS Number: Molecular Weigl	lla: C ₁₀ H ₁₅ N 7632-10-2 ht: 149.23
	Material Characteri	zation Summary	
Analytical Test		Method	Results
Primary Chromatograph	ic Purity by GC/FID Analysis	SP10-0101	99.9%
Secondary Chromatographic Purity by HPLC/UV Analysis		SP10-0102	99.9%
Identity by GC/MS Analy	ysis	SP10-0105	Consistent with Structure
Identity by ¹ H-NMR Ana	lysis	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
Mass Balance Purity Factor			99.89%

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.

Spectral and Physical Data

GC/FID



DB-5ms, 30 m x 0.53 mm ID,
1.5 µm film thickness
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
Cool-on-Column
325°C
FC12131901
March 09, 2020
Time Area %

I Cuk #	Ket Hille	
1	6.17	0.01
2	7.11	0.00
3	9.21	0.00
4	9.51	0.02
5	10.67	0.03
6	11.22	99.88
7	11.52	0.01
8	12.45	0.00
9	12.84	0.01
10	13.43	0.00
11	14.59	0.03
12	15.32	0.00
13	15.74	0.00
14	16.42	0.00
15	16.49	0.00
16	16.67	0.00
17	16.91	0.00
18	17.93	0.00
19	25.01	0.00
20	26.62	0.00

Spectral and Physical Data (cont.)

HPLC/UV



Column:	Ascentis	Express Ph	enyl-He	exyl,
	2.7 μm,	3.0 x 100 r	nm	
Mobile Phas	se: A: Aceto	onitrile		
.	B: 0.1%	Phosphoric	acid in	Water
Gradient:	lime (m	in) % A	% B	-
	0.0	5	95	
	0.5	5	95	
	4.5	70	30	
	6.0	70	30	
	6.1	5	95	
Flow Rate:	0.6 mL/	min		
Wavelength	1: 210 nm			
Sample Nar	ne: FC1213	1901		
Acquired:	Februar	y 18, 2020		
Peak #	Ret Time	Area %		
1	0.68	0.01		
2	2.74	0.01		
3	2.83	0.00		
4	3.06	0.02		
5	3.19	99.89		
6	3.48	0.02		
7	3.57	0.01		
8	3.69	0.03		
9	3.80	0.00		

Residual Solvent Analysis by GC/FID Headspace

FID1 A, (F-002-28-RMM-016 FC12131901 11.85mg.D)	Column:	DB-ALC1 30 m x	0.53 mm,
pA		3 µm film thickn	ess
	Temp Program:	40°C hold 12 mi	n to 220°C at
175-		40°C/min hold 5	.5 min
150 -	Carrier Gas:	Helium	
	Flow Rate:	2.0 mL/min	
125 -	Detector Heater Temp:	250°C	
100	Injector:	Headspace Sampler	
	HS Oven Temp:	60°C	
75	Vial Equilibration:	10 minutes	
50 -	Sample Name:	FC12131901	
25-	Acquired:	February 18, 202	20
0	Peak Compound	Area	Weight %
0 2.5 5 7.5 10 12.5 15 17.5 20 min	1 NMP	NA	NA
	Total		ND

ND- None Detected



GC/MS



Stability

Short term stability studies have been performed in multiple storage conditions for a period of up to four weeks. Short term data is utilized 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 stability findings for a related product (M-112, S(+)-Amphetamine) is listed below.

Storage Condition	Mean Kinetic Temperature (MKT)	Time Period/Result	
Freezer	-15°C		
Refrigerator	4°C	No decrease in purity was noted after	
Room Temperature	21°C	four weeks.	
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	July 16, 2020	Initial version.



Certified Reference Material - Certificate of Analysis

(±)-Methamphetamine-D₅, Primary Measurement Standard

	(±)-1-Phenyl-1,2-dideutero-2-(trideuteromethyl)aminopropane	Cerilliant Quality
Product No.:	M-023-1ML	ISO 17034
Lot No.:	FE01212014	ISO/IEC 17025
Description of CRM:	(\pm) -Methamphetamine-D ₅ in Methanol (Solution)	,
Expiration Date:	February 2025 See Section "Stability Assessment".	ISO 13485
Storage:	Store unopened in freezer (-10 °C to -25 °C).	ISO 14001
Shipping:	Ambient. See Section "Stability Assessment".	ISO 9001
Chemical formula:	$C_{10}H_{10}D_5N$	
CAS No.:	60124-88-1 CHo	
Regulatory:	USDEA Exempt Canadian TK # 61-1291	

Analyte	Certified Concentration ± associated uncertainty U, u=k*u (k=2)	
(±)-Methamphetamine-D $_5$	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 correctConcentration is corrected for chromatographic purity, residual water, 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. For MS Applications, we advise laboratories not to mix lots during a single

Health and safety information:

Accreditation:

nature of any hazard and appropriate precautions to be taken. Cerilliant Corp. is accredited by the US accreditation authority ANAB as registered reference material producer AR-1353 in accordance with ISO 17034 and registered testing laboratory AT-1352 according to ISO/IEC 17025.

Danger. Please refer to the Safety Data Sheet for detailed information about the



sequence.

Darron Ellsworth, Quality Assurance Manager

May 19, 2020 Issue Date

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 17034 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.



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 17034, 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 calculated 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 are analytically 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 C	urve:	Linear Regression
Column:	DB-5ms, 30 m x 0.5	53 mm ID,	Number of Po	oints:	4
	1.5 µm film thickne	SS	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	
		1			

		Vermed Oblicentration (ing/ine)	70K3D - Homogenerty	
Standard Solution	Lot Number	Actual Results	Actual Results	
New Lot	FE01212014	1.010	0.6	
Previous Lot	FE03031704	1.008	0.7	

• 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: Material Lot:	(±)-Methamphetamine-D₅ FC11081601	Chemical Form CAS Number: Molecular Weig	Jla: $C_{10}H_{10}D_5N$ 60124-88-1 ht: 154.26		
	Material Character	rization Summary			
Analytical Test		Method	Res	ults	
Primary Chromatographic	c Purity by GC/FID Analysis	SP10-0101	01 99.9% ¹		
Secondary Chromatograp	phic Purity by HPLC/UV Analysis	SP10-0102	99.7% ¹		
Identity by LC/MS Analys	sis	SP10-0107	Consistent with Structure		
			0.00% D ₀ vs D ₅		
Isotopic Purity and Distri	bution by LC/MS SIM Analysis	SP10-0107	0.00% D_0 to D_2	2.55% D ₄	
			0.01% D ₃	97.44% D ₅	
Identity by ¹ H-NMR Analy	ysis	USP <761>, SP10-0116	Consistent w	ith Structure	
Residual Solvent Analysis	s by GC/FID Headspace	AM1087 ²	None Detected		
Residual Water Analysis	by Karl Fischer Coulometry	AM1346 ²	0.15%		
Mass Balance Purity Fact	or		99.7	/1%	

¹ 0.13% Amphetamine-D₂ detected by GC/FID analysis. 0.18% Amphetamine-D₂ detected by HPLC/UV analysis. 0.29% Amphetamine-D₂ detected by LC/MS analysis.

² 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.
Spectral and Physical Data

GC/FID



Column:	DB-5ms	s, 30 m x 0.53 mm ID),
	1.5 µm	film thickness	
Temp Pro	gram: 40°C to	40°C to 80°C at 40°C/min	
	80°C to	o 175°C at 5°C/min	
	175°C 1	to 300°C at 10°C/min	
	hold 5 i	min	
Injector T	emp: Cool-or	n-Column	
Detector 1	Temp: 325°C		
Sample Na	ame: FC1108	1601	
Sample Na Acquired:	ame: FC1108 April 11	1601 , 2017	
Sample Na Acquired:	ame: FC1108 April 11	1601 , 2017	
Sample Na Acquired: Peak #	ame: FC1108 April 11 Ret Time	1601 , 2017 Area %	
Sample Na Acquired: Peak # 1	ame: FC1108 April 11 <u>Ret Time</u> 9.98	1601 1, 2017 Area % 0.13	
Sample Na Acquired: Peak # 1 2	ame: FC1108 April 11 <u>Ret Time</u> 9.98 11.47	1601 , 2017 Area % 0.13 99.86	
Sample Na Acquired: Peak # 1 2 3	ame: FC1108 April 11 <u>Ret Time</u> 9.98 11.47 13.22	1601 , 2017 Area % 0.13 99.86 0.01	

Peak 1 has been identified as Amphetamine-D₂

HPLC/UV



Column:	Ascentis Express Phenyl-Hexyl, 2.7 µm			
	3.0 x 100 m	m		
Mobile Phase:	A: Acetonitrile			
	B: 0.1% Pho	sphoric	acid	
Gradient:	Time (min)	%A	%В	
	0.0	5	95	
	0.5	5	95	
	4.5	70	30	
	6.0	70	30	
	6.1	5	95	
Flow Rate:	0.6 mL/min			
Wavelength:	210 nm			
Sample Name:	FC11081601			
Acquired:	April 12, 201	17		
Peak # Ret	Fime A	Area %		
1 1	74			

Peak #	Ret Time	Area %
1	1.74	0.05
2	3.17	0.18
3	3.32	99.70
4	3.58	0.04
5	4.08	0.02
6	4.50	0.01

Peak 2 has been identified as Amphetamine-D₂

Residual Solvent Analysis by GC/FID Headspace



¹H NMR



Instrument:

JEOL ECS 400

LC/MS



Isotopic Purity by LC/MS SIM



Certificate Page 9 of 10

Stability

Short term stability studies have been performed in multiple storage conditions for a period of up to four weeks. Short term data is utilized 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 stability findings for a related product (M-034, (\pm) -Methamphetamine-D₈) is listed below.

Storage Condition	Mean Kinetic Temperature (MKT)	Time Period/Result	
Freezer	-15°C		
Refrigerator	4°C	No decrease in purity was noted after	
Room Temperature	21°C	four weeks.	
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	May 19, 2020	Initial version.



Certified Reference Material - Certificate of Analysis

I	Naloxone, Primary Measurement Standard	Cerilliant Quality
('5α)-4,5-Epoxy-3,14-dihydroxy-17-(2-propenyl)morphinan-6-one	ISO 17034
Product No.:	N-004-1ML	ISO/IEC 17025
Lot No.:	FN02212003	100/120 17020
Description of CRM:	Naloxone in Methanol (Solution)	ISO 13485
Expiration Date:	March 2025 See Section "Stability Assessment".	ISO 14001
Storage:	Store unopened in freezer (-10 °C to -25 °C).	ISO 9001
Shipping:	Ambient. See Section "Stability Assessment". HO	
Chemical formula:	C ₁₉ H ₂₁ NO ₄	
CAS No.:	465-65-6	он СН2

Analyte		Certified Concentration \pm associated uncertainty U, u=k*u (k=2)
Naloxone		1.000 ± 0.006 mg/mL
Metrological traceability:	:y: Traceable to the SI and higher order standards from NIST through an unbroken chain of comparisons. See "Details on metrological traceability" 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 μ L for quantitative applications	
Instructions for handling and correct use: Health and safety	Concentration is corrected for chromatographic purity, residual water, 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. Danger, Please refer to the Safety Data Sheet for detailed information about	
information:	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 17034 and registered testing laboratory AT-1352 according to ISO/IEC 17025.	



Darron Ellsworth, Quality Assurance Manager

April 02, 2020

Issue Date

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 17034 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.



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 17034, 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 calculated 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 are analytically 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:	HPLC/UV	Calibration Curve:	Linear Regression
Column:	Ascentis Express Phenyl-Hexyl, 2.7 μm, 3.0 x 50 mm	Number of Points:	4
Mobile Phase:	Acetonitrile:0.1% Phosphoric acid in Water (7:93)	Linearity (r) :	1.000
Flow Rate:	1.5 mL/min		
Wavelength:	225 nm		
	Verified Concentration	on (ma/mL) 9	&RSD - Homogeneity

		Vernica concentration (mg/me)	Jakob Holliogeneity	
Standard Solution	Lot Number	Actual Results	Actual Results	
New Lot	FN02212003	1.019	0.8	
Previous Lot	FN02211902	1.007	0.5	

• 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: Material Lot:	Naloxone FN10141906	Chemical Form CAS Number: Molecular Weig	ula: C ₁₉ H ₂₁ NO ₄ 465-65-6 ght: 327.37
	Material Characte	erization Summary	
Analytical Test		Method	Results
Primary Chromatograph	ic Purity by HPLC/UV Analysis	20384348	99.4%
Secondary Chromatographic Purity by GC/FID Analysis		20384346	99.9%
Identity by LC/MS Analysis		20384217	Consistent with Structure
Identity by ¹ H-NMR Analysis		20384224	Consistent with Structure
Residual Solvent Analysis by GC/FID Headspace		20397799 ¹	0.09%
Residual Water Analysis by Karl Fischer Coulometry		20398075 ¹	Below Quantitation Limit
Inorganic Content by Microash Analysis		20384350	< 0.2%
Mass Balance Purity Fac	tor		99.34%

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.

Spectral and Physical Data

HPLC/UV



GC/FID



Residual Solvent Analysis by GC/FID Headspace



Area %

0.01

0.03

0.00

99.95

0.02



LC/MS



Stability

Short term stability studies have been performed in multiple storage conditions for a period of up to four weeks. Short term data is utilized 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 stability findings for this product is listed below.

Storage Condition	Mean Kinetic Temperature (MKT)	Time Period/Result	
Freezer	-15°C		
Refrigerator	4°C	No decrease in purity was noted after	
Room Temperature	21°C	four weeks.	
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	April 02, 2020	Initial version.



Certified Reference Material - Certificate of Analysis

1	Valoxone-D ₅ , Pri	mary Measurement Star	ndard	Cerilliant Quality
(5	α)-3,14-dihydroxy-17-pi	rop-2-en-1-yl)-4,5-epoxymorphinan-	δ-one-D₅	ISO 17034
Product No.:	N-115-1ML			ISO/IEC 17025
Lot No.:	FN03022013			ISO 13485
Description of CRM	Naloxone-D ₅ in	Methanol (Solution)		150 14001
Expiration Date:	April 2023	See Section "Stability Asses	sment".	130 14001
Storage:	Store unopened	in freezer (-10 °C to -25 °C).		ISO 9001
Shipping:	Ambient.	See Section "Stability Assessment".	HO	
Chemical formula:	$C_{19}H_{16}D_5NO_4$			
CAS No.:	1261079-38-2		O OH	

Analyte	Certified Concentration ± associated uncertainty U, u=k*u (k=2)
Naloxone-D₅	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	Concentration is corrected for chromatographic purity, residual water, residual

 handling and correct
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.
For MS Applications, we advise laboratories not to mix lots during a single sequence.
Health and safety information:
Accreditation:
Cerilliant Corp. is accredited by the US accreditation authority ANAB as registered reference material producer AR-1353 in accordance with ISO 17034

and registered testing laboratory AT-1352 according to ISO/IEC 17025.



Darron Ellsworth, Quality Assurance Manager

May 02, 2020

Issue Date

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 17034 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.



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 17034, 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 calculated 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 are analytically 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:	HPLC/UV		Calibration	Curve:	Linear Regression
Column:	Ascentis Express C1	Number of I	Points:	4	
Mobile Phase:	Acetonitrile: 0.1% Phosphoric acid in Water (8:92)		Linearity (r) : 1.000		1.000
Flow Rate:	1.2 mL/min				
Wavelength:	225 nm				
		Verified Concentration	(mg/mL)	%F	SD - Homogeneity
Standard					

Standard Solution	Lot Number	Actual Results	Actual Results
New Lot	FN03022013	1.016	1.0
Previous Lot	FN02131802	1.015	0.6

 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: Material Lot:	Naloxone-D ₅ FN11261902	Chemical Form CAS Number: Molecular Weig	nula: C ₁₉ H 126 ght: 332	H ₁₆ D₅NO₄ 1079-38-2 .41	
	Material Charact	erization Summary			
Analytical Test		Method	Res	ults	
Primary Chromatograph	ic Purity by HPLC/UV Analysis	20384348	99.9	99.9% ¹	
Secondary Chromatogra	phic Purity by GC/FID Analysis	20384346	> 99	9.9%	
Identity by LC/MS Analysis		20384217	Consistent with Structure		
			0.01%	D ₀ vs D ₅	
Isotopic Purity and Distribution by LC/MS SIM Analysis		20384217	0.01% D_0 to D_2	6.96% D ₄	
			0.23% D ₃	92.78% D ₅	
Identity by ¹ H-NMR Analysis		20384224	Consistent with Structure		
Residual Solvent Analysis by GC/FID Headspace		20397799 ²	0.17%		
Residual Water Analysis by Karl Fischer Coulometry		20398075 ²	Not Detected		
Inorganic Content by Microash Analysis		20384350	< 0.2%		
Mass Balance Purity Fac	tor		99.7	74%	

¹ No Noroxymorphone detected by HPLC/UV analysis.

² 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.

Spectral and Physical Data

HPLC/UV



GC/FID



Column:		DB-5ms, 30 m x 0.53 mm ID, 1.5 µm film thickness		
Temp Progra	am:	40°C to 200°C at 40°C/min		
		200°C	to 280°C at 5°C /	min hold 18 min
Injector Ten	np:	Cool-o	n-Column	
Detector Ter	np:	325°C		
Sample Nam	ne:	FN11261902		
Acquired:		March 13, 2020		
Peak #	Ret T	ime	Area %	
1	11.1	10	0.02	
2	18.	73	99.98	

Residual Solvent Analysis by GC/FID Headspace



Instrument:

JEOL ECS 400

¹H NMR



Certificate Page 7 of 10

Cerilliant Corporation, 811 Paloma Drive, Suite A Round Rock, TX 78665, USA, Tel: 800-848-7837 / 512-238-9974

LC/MS



Isotopic Purity by LC/MS SIM



Stability

Short term stability studies have been performed in multiple storage conditions for a period of up to four weeks. Short term data is utilized 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 stability findings for a related product (N-004, Naloxone) is listed below.

Storage Condition	Mean Kinetic Temperature (MKT)	Time Period/Result			
Freezer	-15°C				
Refrigerator	4°C	No decrease in purity was noted after			
Room Temperature	21°C	four weeks.			
40°C	40°C				
<i>Transport/Shipping:</i> 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 41 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	May 02, 2020	Initial version.



Certified Reference Material - Certificate of Analysis

	Oxycodone, Primary Measurement Standard	Cerilliant Quality		
4,5-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one				
Product No.:	O-002-1ML	ISO/IEC 17025		
Lot No.:	FE01082008	ISO 13485		
Description of CRM	: Oxycodone in Methanol (Solution)	ISO 14001		
Expiration Date:	January 2025 See Section "Stability Assessment".	ISO 9001		
Storage:	Store unopened in freezer (-10 °C to -25 °C).			
Shipping:	Ambient. See Section "Stability Assessment".			
Chemical formula:	C ₁₈ H ₂₁ NO ₄			
CAS No.:	76-42-6 O			
Regulatory:	USDEA Exempt Canadian TK # 61-1414	онсн³		

Analyte	Certified Concentration ± associated uncertainty U, u=k*u (k=2)
Oxycodone	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 water, 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 17034 and registered testing laboratory AT-1352 according to ISO/IEC 17025.



Det

Darron Ellsworth, Quality Assurance Manager

July 29, 2020 Issue Date

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 17034 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.



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 17034, 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 calculated 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 are analytically 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:	HPLC/UV		Calibration Curve: Linear Regres		Linear Regression
Column:	Ascentis Express C1	Number of F	oints:	4	
Mobile Phase:	Acetonitrile:0.1% Phosphoric acid in Water (10:90)		Linearity (r) : 1.000		1.000
Flow Rate:	1.5 mL/min				
Wavelength:	230 nm				
		Verified Concentration	i (mg/mL)	%F	RSD - Homogeneity
Standard					

Standard Solution	Lot Number	Actual Results	Actual Results
New Lot	FE01082008	0.995	1.5
Previous Lot	FE08241701	0.999	0.6

• 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: Material Lot:	Oxycodone PC04111701	Chemical Form CAS Number: Molecular Weig	aula: C ₁₈ H ₂₁ NO ₄ 76-42-6 ght: 315.36
	Material Charact	erization Summary	
Analytical Test		Method	Results
Primary Chromatographi	ic Purity by HPLC/UV Analysis	SP10-0102	99.8%
Secondary Chromatographic Purity by GC/FID Analysis		SP10-0101	99.9%
Identity by GC/MS Analysis		SP10-0105	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	Below Quantitation Limit
Residual Water Analysis by Karl Fischer Coulometry		AM1346 ¹ Below Quantitation L	
Inorganic Content by Microash Analysis		SP10-0135	< 0.2%
Mass Balance Purity Fac	tor		99.82%

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.

Spectral and Physical Data

HPLC/UV



Column:	Ascentis	Ascentis Express C18, 2.7 µm,			
	3.0 x 10	3.0 x 100 mm			
Mobile Phas	e: A: Acete	A: Acetonitrile			
	B: 0.05	% Phosphor	ic acid i	n Water	
Gradient:	Time (m	nin) % A	% B	-	
	0.0	5	95		
	0.5	5	95		
	7.0	65	35		
	8.0	65	35		
	8.1	5	95		
Flow Rate:	0.6 mL/	'min			
Wavelength	: 230 nm				
Sample Nam	ne: PC0411	1701			
Acquired:	March 2	5, 2019			
Peak #	Ret Time	۵rea %			
1	2.05	0.01			
2	2.32	0.01			
3	2.62	0.03			
4	2.93	0.02			
5	3.40	99.81			
6	3.62	0.03			
7	3.67	0.02			
8	3.74	0.00			
9	3.77	0.02			
10	3.82	0.00			
11	3.88	0.00			
12	3.97	0.01			
13	3.99	0.01			
14	4.12	0.01			
15	4.19	0.01			
16	4.25	0.00			
17	4.51	0.01			
18	5.25	0.01			
19	5.71	0.00			

GC/FID



Column:	DB-5ms, 30 m x 0.53 mm ID,			
	1.5 j	um film thickness		
Temp Progr	am: 40°C	40°C to 200°C at 40°C/min		
	200°	C to 280°C at 5°C/min		
	hold	hold 18 min		
Injector Ter	mp: Cool	-on-Column		
Detector Te	mp: 325°	С		
Sample Nan	ne: PCO4	111701		
Acquired:	April	April 24, 2017		
Peak #	Ret Time	Area %		
1	15.76	0.02		
2	16.57	0.04		
3	16.89	99.93		
4	18.94	0.02		

Residual Solvent Analysis by GC/FID Headspace PD1A Foot Signal (F2017-04-26-12-33-27-RM0-004 PC04111701.D) Co



Column:		DB-ALC1 30 m x 0.53 mm,		
		3 µm film thickr	ness	
Temp Program:		40°C hold 12 min to 220°C at		
		40°C/min hold §	5.5 min	
Carrier G	as:	Helium		
Flow Rat	e:	2.0 mL/min		
Detector	Heater Temp:	250°C		
Injector:		Headspace Sam	pler	
HS Oven Temp:		60°C		
Vial Equilibration:		10 minutes		
Sample N	lame:	PC04111701		
Acquired	:	April 26, 2017		
Peak	Compound	Area	Weight %	
1	Ethyl ether	9.82	BQL	
2	NMP	NA	NA	
Total			BQL	
	BQL - Below Quantitation Limit			



GC/MS



Stability

Short term stability studies have been performed in multiple storage conditions for a period of up to four weeks. Short term data is utilized 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 stability findings for this product is listed below.

Storage Condition Mean Kinetic Temperature (MKT)		Time Period/Result	
Freezer	-15°C		
Refrigerator 4°C		No decrease in purity was noted after	
Room Temperature	21°C	four weeks.	
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	July 29, 2020	Initial version.



Certified Reference Material - Certificate of Analysis

Oxycodone-D ₆ , Primary Measurement Standard					
4,5-Epoxy-14-ł	4,5-Epoxy-14-hydroxy-3-trideuteromethoxy-17-[trideuteromethyl]morphinan-6-one				
Product No.:	O-008-1ML		ISO/IEC 17025		
Lot No.:	FE02042002		ISO 13485		
Description of CRM:	Oxycodone-D ₆	in Methanol (Solution)	150 14001		
Expiration Date:	March 2025	See Section "Stability Assessment".	130 14001		
Storage:	Store unopene	d in freezer (-10 °C to -25 °C).	ISO 9001		
Shipping:	Ambient.	See Section "Stability Assessment".			
Chemical formula:	$C_{18}H_{15}D_6NO_4$	230			
CAS No.:	152477-91-3	o [/-			
Regulatory:	USDEA Exemp	t Canadian TK # 61-1420	OH CD3		

Analyte	Certified Concentration ± associated uncertainty U, u=k*u (k=2)
Oxycodone-D ₆	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	Concentration is corrected for chromatographic purity, residual water, residual solvents, and residual inorganics. No adjustment required before use.
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.
	For MS Applications, we advise laboratories not to mix lots during a single sequence.
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 17034 and registered testing laboratory AT-1352 according to ISO/IEC 17025.



Darron Ellsworth, Quality Assurance Manager

April 13, 2020

Issue Date
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 17034 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.



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 17034, 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 calculated 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 are analytically 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:	HPLC/UV		Calibration	Curve:	Linear Regression
Column:	Ascentis Express C18, 2.7 µm, 3.0 x 100 mm		Number of I	Points:	4
Mobile Phase:	Acetonitrile: 0.1% Phosphoric acid in Water (10:90)		Linearity (r) : 1.000		1.000
Flow Rate:	1.5 mL/min				
Wavelength:	225 nm				
		Verified Concentration	(mg/mL)	%R	SD - Homogeneity
Standard					

Standard Solution	Lot Number	Actual Results	Actual Results
New Lot	FE02042002	0.999	1.3
Previous Lot	FE05191703	1.008	0.6

 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:Oxycodone-D6Chemical FormMaterial Lot:FC12181501CAS Number:Molecular Weig		nula: C ₁₈ F 152 ght: 321	I ₁₅ D ₆ NO₄ 477-91-3 40	
	Material Charact	erization Summary		
Analytical Test		Method	Res	ults
Primary Chromatographi	c Purity by HPLC/UV Analysis	20384348	99.	8%
Secondary Chromatogra	phic Purity by GC/FID Analysis	20384346	99.	9%
Identity by LC/MS Analys	sis	20384217	Consistent w	ith Structure
			0.03% [D ₀ vs D ₆
		20384217	0.03% D ₀	0.18% D ₄
Isotopic Purity and Distri	Idution by LC/MS SIM Analysis		0.01% D_1 to D_2	0.77% D ₅
			0.20% D ₃	98.80% D ₆
Identity by ¹ H-NMR Analysis		20384224	Consistent w	ith Structure
Residual Solvent Analysis by GC/FID Headspace		20397799 ¹	None D	etected
Residual Water Analysis by Karl Fischer Coulometry		20398075 ¹	Not Detected	
Inorganic Content by Microash Analysis		20384350	< 0.2%	
Mass Balance Purity Fact	tor		99.7	16%

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.

Spectral and Physical Data

HPLC/UV



8

9

10

11

5.78

6.05

6.20

6.24

0.03

0.01

0.02

0.01

GC/FID



Column:	DB-35n	ns, 30 m x 0.53 mm l	D,
	1.0 µm	film thickness	
Temp Prog	ram: 40°C to	200°C at 40°C/min	
	200°C	to 280°C at 5°C/min	
	hold 18	min	
Injector Te	mp: Cool-or	n-Column	
Detector Te	emp: 325°C		
Sample Na	me: FC1218	1501	
Acquired:	March 2	22, 2016	
•			
•			
Peak #	Ret Time	Area %	
Peak #	Ret Time 14.84	Area % 0.00	
Peak #	Ret Time 14.84 18.19	Area % 0.00 0.11	
Peak #	Ret Time 14.84 18.19 18.54	Area % 0.00 0.11 99.85	
Peak #	Ret Time 14.84 18.19 18.54 21.26	Area % 0.00 0.11 99.85 0.01	
Peak # 1 2 3 4 5	Ret Time 14.84 18.19 18.54 21.26 22.33	Area % 0.00 0.11 99.85 0.01 0.00	
Peak #	Ret Time 14.84 18.19 18.54 21.26 22.33 23.25	Area % 0.00 0.11 99.85 0.01 0.00 0.01	
Peak # 1 2 3 4 5 6 7	Ret Time 14.84 18.19 18.54 21.26 22.33 23.25 24.37	Area % 0.00 0.11 99.85 0.01 0.00 0.01 0.01	

Residual Solvent Analysis by GC/FID Headspace

FID1 A, (F-002-28-RMO-006 FC12181601 10.21mg.D)	Column:		DB-ALC1 30 n	n x 0.53 mm,
Nom.] 200-			3 µm film thic	kness
	Temp Pro	ogram:	40°C hold 12	min to 220°C at
175-			40°C/min holo	d 5.5 min
	Carrier G	as:	Helium	
150 -	Flow Rate	e:	2.0 mL/min	
125	Detector	Heater Temp:	250°C	
	Injector:		Headspace Sa	mpler
100 -	HS Oven	Temp:	60°C	
	Vial Equil	libration:	10 minutes	
75				
50	Sample N	lame:	FC12181501	
	Acquired	:	February 21, 2	2020
25-				
	Peak	Compound	Area	Weight %
0-	1	NMP	NA	NA
	Total			ND

ND - None Detected



LC/MS



Isotopic Purity by LC/MS SIM



Stability

Short term stability studies have been performed in multiple storage conditions for a period of up to four weeks. Short term data is utilized 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 stability findings for a related product (O-042, Oxycodone-D₃) is listed below.

Storage Condition	Mean Kinetic Temperature (MKT)	Time Period/Result		
Freezer	-15°C			
Refrigerator	4°C	No decrease in purity was noted after		
Room Temperature	21°C	four weeks.		
40°C	40°C			
<i>Transport/Shipping:</i> 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	April 13, 2020	Initial version.



Certified Reference Material - Certificate of Analysis

Oxymo	orphone, Primary Measurement Standard	Cerilliant Quality
5α	u-4,5-Epoxy-3,14-dihydroxy-17-methylmorphinan-6-one	ISO 17034
Product No.:	O-004-1ML	ISO/IEC 17025
Lot No.:	FE01082009	130/120 17025
Description of CRM:	Oxymorphone in Methanol (Solution)	ISO 13485
Expiration Date:	January 2025 See Section "Stability Assessment".	ISO 14001
Storage:	Store unopened in freezer (-10 °C to -25 °C).	ISO 9001
Shipping:	Ambient. See Section "Stability Assessment".	
Chemical formula:	C ₁₇ H ₁₉ NO ₄	\checkmark
CAS No.:	76-41-5 0	
Regulatory:	USDEA Exempt Canadian TK # 61-1416	OH CH3

Analyte		Certified Concentration \pm associated uncertainty U, $u=k*u$ (k=2)	
Oxymorpho	ne	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:	$1 \ \mu L$ for quantitat	ive applications	
Instructions for handling and correct use: Health and safety	Concentration is of solvents, and resi Users should quar laboratory practic concentration. Ea Danger. Please re	tration is corrected for chromatographic purity, residual water, residual s, and residual inorganics. No adjustment required before use. should quantitatively transfer desired volume using established good ory practices to spike into matrix or to dilute to the desired tration. Each ampoule is intended for one-time use.	
information:	the nature of any hazard and appropriate precautions to be taken.		
Accreditation:	Cerilliant Corp. is registered referent and registered test	accredited by the US accreditation authority ANAB as needed and the accreditation authority ANAB as needed accordance with ISO 17034 sting laboratory AT-1352 according to ISO/IEC 17025.	



Darron Ellsworth, Quality Assurance Manager

February 20, 2020

Issue Date

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 17034 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.



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 17034, 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 calculated 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 are analytically 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:	HPLC/UV	Calibration Curve:	Linear Regression
Column:	Ascentis Express Phenyl-Hexyl, 2.7 μm, 3.0 x 100 mm	Number of Points:	4
Mobile Phase:	Acetonitrile:0.1% Phosphoric acid in Water (5:95)	Linearity (r) :	1.000
Flow Rate:	1.5 mL/min		
Wavelength:	225 nm		
	Verified Concentration	on (mg/mL) 9	&RSD - Homogeneity

		Vernica concentration (mg/me)	/oron inolinogeneity	
Standard Solution	Lot Number	Actual Results	Actual Results	
New Lot	FE01082009	1.001	0.6	
Previous Lot	FE03201901	0.999	0.4	

• 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: Material Lot:	Oxymorphone FC05021701	Chemical Form CAS Number: Molecular Weig	ula: C ₁₇ H ₁₉ NO ₄ 76-41-5 ght: 301.34
	Material Characte	erization Summary	
Analytical Test		Method	Results
Primary Chromatograph	ic Purity by HPLC/UV Analysis	SP10-0102	99.8%
Secondary Chromatographic Purity by GC/FID Analysis		SP10-0101	> 99.9%
Identity by LC/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	0.14%
Residual Water Analysis by Karl Fischer Coulometry		AM1346 ¹	Below Quantitation Limit
Inorganic Content by Microash Analysis		SP10-0135	< 0.2%
Mass Balance Purity Fac	tor		99.65%

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.

Spectral and Physical Data

HPLC/UV



Column:	Ac 2.	Acentis Express Phenyl-Hexyl, 2.7 um, 3.0 x 100 mm				
Mobile Ph	ase: A:	A: Acetonitrile				
	B:	0.1% Ph	osphor	ic acid in	Water	
Gradient:	Tir	ne (min)	% A	% B		
		0.0	2	98	-	
		0.5	2	98		
		4.0	15	85		
		7.0	50	50		
		9.0	50	50		
		9.1	2	98		
Flow Rate	: 1.0	0 mL/min				
Waveleng	th: 22	5 nm				
Sample Name: Acquired:		:0502170: Igust 02,	1 2017			
Peak #	Ret Time	Area o	%			
1	1.69	0.09				
2	1.78	0.12				
3	2.62	99.66	5			
4	3.02	0.04				
5	3.12	0.03				
6	4.55	0.06				
7	4.84	0.02				

GC/FID



Column: Temp Program:		DB-5ms, 30 m x 0.53 mm ID, 1.5 µm film thickness 40°C to 200°C at 40°C/min 200°C to 280°C at 5°C/min hold 18 min		
Injector Temp: Detector Temp:		Cool-on-Column 325°C		
Sample Name: Acquired:		FC05021701 July 11, 2017		
Peak #	Ret Tim	e Area %		
1	4.62	0.06		
2	17.32	99.94		

Residual Solvent Analysis by GC/FID Headspace



¹H NMR





LC/MS

Column: Mobile Phase:	Ascentis Exp A: 0.1% For B: Acetonitri	ress C1 mic acio le	8, 2.7 μr 1 in Wate	, 3.0 x 50 mm Flow Rate: Scan Range: Ionization:	0.4 mL/min 100 - 1200 amu Electrospray, Positive Ion
Gradient:	Time (min)	% A	% B	Instrument:	Waters XEVO G2 QTOF
	0.0	99	1	Acquired:	July 11, 2017
	0.5	99	1		
	4.0	95	5		
	5.8	95	5		
	6.0	99	1		
	8.0	99	1		



Stability

Short term stability studies have been performed in multiple storage conditions for a period of up to four weeks. Short term data is utilized 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 stability findings for a related product (O-003, Oxymorphone- D_3) is listed below.

Storage Condition	Mean Kinetic Temperature (MKT)	Time Period/Result	
Freezer	-15°C		
Refrigerator	4°C	No decrease in purity was noted after	
Room Temperature	21°C	four weeks.	
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	February 20, 2020	Initial version.



Certified Reference Material - Certificate of Analysis

Oxymorphone-D ₃ , Primary Measurement Standard Cerilliant				
(5α-	4,5-Epoxy-3,14-dihy	droxy-17-trideuteromethylmorphinan-	6-one	ISO 17034
Product No.:	O-019-1ML			ISO/IEC 17025
Lot No.:	FE01082010			ISO 13485
Description of CRM:	Oxymorphone-[D_3 in Methanol (Solution)		150 14001
Expiration Date:	January 2025	See Section "Stability Asses	sment".	150 14001
Storage:	Store unopened	in freezer (-10 °C to -25 °C).	HO o	ISO 9001
Shipping:	Ambient.	See Section "Stability Assessment".		
Chemical formula:	$C_{17}H_{16}D_3NO_4$		人	<u>`</u>
CAS No.:	145225-03-2		° 🖌	Σ.
Regulatory:	USDEA Exempt	Canadian TK # 61-1421	.	OH CD3

Analyte	Certified Concentration \pm associated uncertainty U, $u=k*u$ (k=2)
Oxymorphone-D ₃	$1.000 \pm 0.006 \text{ mg/mL}$

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 Concentration is corrected for chromatographic purity, residual water, residual solvents, and residual inorganics. No adjustment required before use. handling and correct Users should quantitatively transfer desired volume using established good use: laboratory practices to spike into matrix or to dilute to the desired concentration. Each ampoule is intended for one-time use. For MS Applications, we advise laboratories not to mix lots during a single sequence. Health and safety Danger. Please refer to the Safety Data Sheet for detailed information about information: the nature of any hazard and appropriate precautions to be taken. Cerilliant Corp. is accredited by the US accreditation authority ANAB as Accreditation: registered reference material producer AR-1353 in accordance with ISO 17034 and registered testing laboratory AT-1352 according to ISO/IEC 17025.



Darron Ellsworth, Quality Assurance Manager

February 18, 2020

Issue Date

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 17034 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.



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 17034, 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 calculated 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 are analytically 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:	HPLC/UV		Calibration	Curve:	Linear Regression
Column:	Ascentis Express Phenyl-Hexyl, 2.7 um, 3.0 x 100 mm		Number of Points: 4		4
Mobile Phase:	Acetonitrile:0.1% Phosphoric acid in Water (5:95)		Linearity (r) : 1.000		1.000
Flow Rate:	1.5 mL/min				
Wavelength:	225 nm				
		Verified Concentratio	n (mg/mL)	%F	RSD - Homogeneity

		· · · · · · · · · · · · · · · · · · ·	,
Standard Solution	Lot Number	Actual Results	Actual Results
New Lot	FE01082010	0.992	0.5
Previous Lot	FE07311802	0.998	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.

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: Material Lot:	Material Name:Oxymorphone-D3Material Lot:FC03151801		nula: C ₁₇ 145 ght: 304	H ₁₆ D₃NO₄ 5225-03-2 I.36
	Material Character	rization Summary		
Analytical Test		Method	Results	
Primary Chromatograph	ic Purity by HPLC/UV Analysis	SP10-0102	99.	8% ¹
Secondary Chromatogra	phic Purity by GC/FID Analysis	SP10-0101	99	.4%
Identity by LC/MS Analy	sis	SP10-0107	Consistent with Structure	
			0.17%	D ₀ vs D ₃
Isotopic Purity and Distr	ibution by LC/MS SIM Analysis	SP10-0107	0.16% D ₀	0.24% D ₂
			0.05% D ₁	99.55% D ₃
Identity by ¹ H-NMR Ana	lysis	USP <761>, SP10-0116	Consistent v	vith Structure
Residual Solvent Analysi	is by GC/FID Headspace	AM1087 ²	None Detected	
Residual Water Analysis	by Karl Fischer Coulometry	AM1346 ²	Below Quantitation Limit	
Inorganic Content by Mi	croash Analysis	SP10-0135	< 0.2%	
Mass Balance Purity Fac	tor		99.	79%

¹ 0.02% Noroxymorphone detected by HPLC/UV analysis.

² 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.

Spectral and Physical Data

HPLC/UV



Column:		Ascentis	Express Pł	nenyl-He	xyl,
		2.7 µm, 3	3.0 x 100 i	mm	
Mobile Phase:		A: Acetor	nitrile		
		B: 0.1%	Phosphori	c acid in	Water
Gradient:		Time (mi	п) % A	% B	
		0.0	2	98	
		0.5	2	98	
		4.0	15	85	
		7.0	50	50	
		9.0	50	50	
		9.1	2	98	
Flow Rate	:	0.8 mL/n	nin		
Waveleng	th:	225 nm			
Sample Na	ame:	FC03151	801		
Acquired:		Decembe	r 05, 2018	3	
Book #	Dot 1	Timo	Aroz 0/a		
1 Peak #	2	70	00 72		
1	2.	70 10	99.72		
2	з. э	12	0.17		
3). 2	+9 67	0.01		
4	.د م	07 DE	0.01		
5	4.	20	0.02		
0	4.	00 00	0.01		
/	4.0 E	44	0.00		
0	5.4	+4 51	0.01		
9	5. E	04 C 4	0.01		
10	5.0 E	04 05	0.05		
11	э.	90	0.00		

Peak #5 has been identified as Noroxymorphone

GC/FID



Column:	DB-35	oms, 30 m x 0.53 mm ID,		
Temp Pro	gram: 40°C 200°C hold 1	40°C to 200°C at 40°C/min 200°C to 280°C at 5°C/min hold 18 min		
Injector T	emp: Cool-o	on-Column		
Detector	Temp: 325°C			
Sample N Acquired:	ame: FC031 Nover	.51801 nber 21, 2018		
Peak #	Ret Time	Area %		
1	3.90	0.31		
2	4.22	0.12		
3	4.38	0.02		
4	4.51	0.07		
5	9.77	0.03		
6	18.77	0.02		

99.43

Residual Solvent Analysis by GC/FID Headspace



7

19.76



O-019-1ML Revision 00

LC/MS

Column: Ascentis Express C18, 2.7 µm, 0.4 mL/min Flow Rate: 3.0 x 50 mm 100-1200 amu Scan Range: A: 0.1% Formic acid in Water **Mobile Phase:** Ionization: Electrospray, Positive Ion **B:** Acetonitrile Instrument: Waters XEVO G2 QTOF Gradient: Time (min) % A % B Acquired: November 26, 2018 0.0 98 2 0.5 2 98 4.0 70 30 5.8 70 30 6.0 98 2 8.0 98 2 RMO-008 FC03151801 Oxymorphone-D3 Cone Voltage: 15.0000000 W11261835 426 (1.617) Cm (420:429) 1: TOF MS ES+ 305.1577 1.54e6 100-Theoretical [M + H]+: 305.1581 Found [M + H]⁺: 305.1577 % 306.1612 631.2922 ,307.1639 0+ - m/z 100 200 300 400 500 600 700 800 900 1000 1100

Isotopic Purity by LC/MS SIM

Column:	Ascentis Express C18, 2.7 µm, 3.0 x 50 mm		Flow Rate: Scan Range:	0.4 mL/min 302-305 amu	
Mobile Phase:	A: 0.1% Formic acid in Water		Ionization:	Electrospray, Positive Ion	
	B: Acetonitri	le		Instrument:	Waters XEVO G2 QTOF
Gradient:	Time (min)	% A	% B	Acquired:	November 26, 2018
	0.0	98	2		
	0.5	98	2		
	4.0	70	30		
	5.8	70	30		
	6.0	98	2		
	8.0	98	2		



Cerilliant Corporation, 811 Paloma Drive, Suite A Round Rock, TX 78665, USA, Tel: 800-848-7837 / 512-238-9974

Stability

Short term stability studies have been performed in multiple storage conditions for a period of up to four weeks. Short term data is utilized 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 stability findings for this product is listed below.

Storage Condition	Mean Kinetic Temperature (MKT)	Time Period/Result	
Freezer	-15°C		
Refrigerator	4°C	No decrease in purity was noted after	
Room Temperature	ture 21°C four weeks.		
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	February 18, 2020	Initial version.



Certified Reference Material - Certificate of Analysis



Analyte	Certified Concentration ± associated uncertainty U, u=k*u (k=2)
(-)-∆ ⁹ -THC	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 water, 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 17034 and registered testing laboratory AT-1352 according to ISO/IEC 17025.



Darron Ellsworth, Quality Assurance Manager

May 01, 2020

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 17034 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.



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 17034, 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 calculated 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 are analytically 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:	HPLC/UV	Calibration Curve:	Linear Regression
Column:	Luna C18 (2), 3 µm, 4.6 x 150 mm	Number of Points:	4
Mobile Phase:	Methanol:Water:Tetrahydrofuran (71:24:5)	Linearity (r) :	1.000
Flow Rate:	1.0 mL/min		
Wavelength:	228 nm		

		Verified Concentration (mg/mL)	%RSD - Homogeneity
Standard Solution	Lot Number	Actual Results	Actual Results
New Lot	FE02072002	0.986	0.5
Previous Lot	FE08221804	0.948	0.1

- 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.

Standard Solution	Lot Number	Verified Concentration against USP Standard HPLC Analysis			
New Lot	FE02072002	1.018			
 Concentration is verified against an independently prepared calibration solution using USP Standard 1651621 Lot R045H0 					

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: Material Lot:	(-)-∆ ⁹ -THC FC02181901	Chemical Form CAS Number: Molecular Weig	nula: $C_{21}H_{30}O_2$ 1972-08-3 ght: 314.46			
Material Characterization Summary						
Analytical Test		Method	Results			
Chromatographic Purity by HPLC/UV Analysis		AM1280	99 .0% ¹			
exo-THC Determination by GC/FID Analysis		AM1266	0.1%			
Identity by GC/MS Analysis		SP10-0105	Consistent with Structure			
Identity by ¹ H-NMR Analysis		USP <761>, SP10-0116	Consistent with Structure			
Residual Solvent Analysis by GC/FID Headspace		AM1087 ²	0.22%			
Residual Water Analysis by Karl Fischer Coulometry		AM1346 ²	0.32%			
Mass Balance Purity Fact	98.51%					
¹ Purity value adjusted for known impurities as shown on the trace below. ² Validated analytical method						

² Validated analytical method

• The chromatographic purity value is used to calculate the Mass Balance Purity Factor.

 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.

Spectral and Physical Data

HPLC/UV



Column: Mobile Phase Flow Rate: Wavelength: Sample Nam Acquired:	Luna (Metha (71:24 1.0 ml 228 nr e: FC021 Septer	Luna C18, 3 µm, 4.6 x 150 mm Methanol:Water:Tetrahydrofuran (71:24:5) 1.0 mL/min 228 nm FC02181901 September 23, 2019			
Peak #	Ret Time	Area %	_		
1	6.85	0.02			
2	8.90	0.14			
3	10.53	0.13			
4	12.08	0.01			
5	12.77	0.02			
6	13.35	0.02			
7	15.96	0.05	Cannabidiol		
8	22.16	0.09			
9	25.42	0.04			
10	27.97	0.51	Cannabinol		
11	29.36	0.00			
12	31.16	0.00			
13	32.42	0.10			
14	35.66	98.72	(-)-∆ ⁹ -THC		
15	39.03	0.09			
16	41.09	0.02	(-)-∆ ⁸ -THC		
17	41.27	0.02			




Column: Temp Progra Injector Ten Detector Ten Sample Nam	DB-35 1.0 µn am: 60°C t 200°C hold 7 np: Cool-o mp: 325°C pe: EC021	DB-35ms, 30 m x 0.53 mm ID, 1.0 µm film thickness 60°C to 200°C at 10°C/min 200°C to 280°C at 5°C/min hold 7 min Cool-on-Column 325°C		
Acquired:	Septer	mber 25, 20	019	
Peak #	Ret Time	Area %	_	
1	22.97	0.03		
2	23.96	0.05	exo-THC	
3	24.32	0.20		
4	24.77	99.44	(-)-∆ ⁹ -THC	
5	25.61	0.04		
6	25.79	0.20		
7	26.10	0.03		

Residual Solvent Analysis by GC/FID Headspace

	Column:	DB-ALC1 30 m	n x 0.53 mm,
FID1 A, (F-002-22-T-005STK FC02181901 8.49mg.D) Nerm,]		3 µm film thic	kness
200 -	Temp Program:	40°C hold 12	min to 220°C at
175-		40°C/min hold	d 5.5 min
	Carrier Gas:	Helium	
150-]	Flow Rate:	2.0 mL/min	
105	Detector Heater Temp:	250°C	
	Injector:	Headspace Sa	mpler
100-	HS Oven Temp:	60°C	
	Vial Equilibration:	10 minutes	
50-j	Sample Name:	FC02181901	
₩ 	Acquired:	September 13	, 2019
0-	Peak Compound	Area	Weight %
	1 Methanol	20.94	0.22
	2 NMP	NA	NA
	Total		0.22



GC/MS



Stability

Short term stability studies have been performed in multiple storage conditions for a period of up to four weeks. Short term data is utilized 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 stability findings for this product is listed below.

Storage Condition	Mean Kinetic Temperature (MKT)	Time Period/Result	
Freezer	-15°C		
Refrigerator	4°C	No decrease in purity was noted after	
Room Temperature	21°C	four weeks.	
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	May 01, 2020	Initial version.



Certified Reference Material - Certificate of Analysis

(-)-Δ ⁹ -	THC-D ₃ , Prin	nary Measurement Standard	Cerilliant Quality
6aR,10aR)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-(pentyl-5,5,5-d ₃)-6H-dibenzo[b,d]pyran-1-ol			ISO 17034
Product No.:	T-011-1ML		ISO/IEC 17025
Lot No.:	FE02042012		ISO 13485
Description of CRM:	$(-)-\Delta^9$ -THC-D ₃ in I	Methanol (Solution)	ISO 14001
Expiration Date:	May 2025	See Section "Stability Assessment".	ISO 9001
Storage:	Store unopened ir	n freezer (-10 °C to -25 °C).	
Shipping:	Ambient. Se	e Section "Stability Assessment".	
Chemical formula:	$C_{21}H_{27}D_{3}O_{2}$	OH	
CAS No.:	81586-39-2		
Regulatory:	USDEA Exempt 0	Canadian TK # 61-1546	CD ₂
		H ₃ C	003
Analyte		Certified Concentration ± associated unc u=k*u (k=2)	ertainty U,
(-)-Δ ⁹ -THC-	·D ₃	$1.000 \pm 0.006 \text{ mg/mL}$	
Metrological traceability:	Traceable to the S chain of comparis	SI and higher order standards from NIST through ar ons. See "Details on metrological traceability" on particular states on the particular states and the particular states and the particular states are states and the particular states are states and the particular states are	n unbroken age 2.
Measurement method:	The certified value characterized star page 2.	e is calculated from high precision weighing of thore ting material. See "Details about certification proce	oughly ss″ on
Intended use:	This Certified Refe calibration, and quality applications. Not s	erence Material is suitable for the in vitro identificat uantification of the analyte(s) in analytical and R&D suitable for human or animal consumption.	ion,
Minimum sample size:	1 μL for quantitati	ive applications	
Instructions for handling and correct	Concentration is c solvents, and resi	corrected for chromatographic purity, residual water dual inorganics. No adjustment required before use	, residual
use:	laboratory practic concentration. Eac	es to spike into matrix or to dilute to the desired ch ampoule is intended for one-time use.	i good
	For MS Application	ns, we advise laboratories not to mix lots during a s	single
Health and safety information:	Danger. Please re the nature of any	fer to the Safety Data Sheet for detailed informatio hazard and appropriate precautions to be taken.	n about
Accreditation:	Cerilliant Corp. is registered referen and registered tes	accredited by the US accreditation authority ANAB acc material producer AR-1353 in accordance with Is sting laboratory AT-1352 according to ISO/IEC 1702	as SO 17034 25.



Darron Ellsworth, Quality Assurance Manager

June 01, 2020 Issue Date

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 17034 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.



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 17034, 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 calculated 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 are analytically 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:	HPLC/UV		Calibration Cur	ve: Linear Regression
Column:	Ascentis Express Pl	nenyl-Hexyl, 2.7 µm,	Number of Poin	its: 4
	3.0 x 100 mm		Linearity (r) :	1.000
Mobile Phase:	Acetonitrile:0.1% F (70:30)	hosphoric acid in Water		
Flow Rate:	1.5 mL/min			
Wavelength:	228 nm			
		Verified Concentration	(mg/mL)	%RSD - Homogeneity
Standard				

Standard Solution	Lot Number	Actual Results	Actual Results
New Lot	FE02042012	0.996	0.1
Previous Lot	FE04231905	0.981	0.1

• 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: Material Lot:	(-)-Δ ⁹ -THC-D ₃ FC10041904	Chemical Formul CAS Number: Molecular Weigh	la: C ₂₁ H ₂₇ D ₃ O ₂ 81586-39-2 t: 317.48
	Material Characte	erization Summary	
Analytical Test		Method	Results
Chromatographic Purity	by HPLC/UV Analysis	20397996	98.8% ¹
exo-THC Determination	by GC/FID Analysis	20397988	0.1%
Identity by GC/MS Anal	ysis	20384214	Consistent with Structure
Identity by ¹ H-NMR Ana	lysis	20384224	Consistent with Structure
Residual Solvent Analys	is by GC/FID Headspace	20397799 ²	1.34%
Residual Water Analysis	by Karl Fischer Coulometry	20398075 ²	Below Quantitation Limit
Mass Balance Purity Fac	tor		97.49%
¹ Purity value adjusted for known impurities as shown on the trace below. ² Validated analytical method			

• The primary chromatographic purity value is used to calculate the Mass Balance Purity Factor.

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.

Spectral and Physical Data

HPLC/UV



olumn: Iobile Pha Iow Rate: /avelengtl ample Nat	Luna se: Metha (71:2 1.0 m h: 228 n me: FC100 Fabru	Luna C18, 3 µm, 4.6 x 150 mm Methanol:Water:Tetrahydrofuran (71:24:5) 1.0 mL/min 228 nm FC10041904		
cquireu:	Герги	aiy 10, 2020		
Peak #	Ret Time	Area %	_	
1	3.71	0.00		
2	4.11	0.00		
3	6.76	0.00		
4	7.44	0.00		
5	8.76	0.07		
6	10.34	0.04		
/	11.60	0.01		
8	12.51	0.01		
9	13.92	0.00		
10	15.72	0.01	Cannabidiol	
11	16.81	0.00		
12	21.84	0.02		
13	23.30	0.00		
14	24.97	0.02		
15	27.48	0.46	Cannabinol	
16	28.68	0.03		
1/	30.40	0.02		
18	31.84	0.13		
19	34.87	98.53	$(-)-\Delta^2$ -THC	
20	38.29	0.19		
21	40.34	0.40	(-)-∆°-1HC	
22	60.97	0.04		

exo-THC by GC/FID



Column: Temp Prog Injector Te Detector T	DB-5 1.5 2009 hold cmp: Cool emp: 3259	DB-5ms, 30 m x 0.53 mm II 1.5 µm film thickness 60°C to 200°C at 10°C/min 200°C to 280°C at 5°C/min hold 7 min Cool-on-Column 325°C	
Sample Na Acquired:	me: FC10 Febr	041904 uary 11, 2020	
Peak #	Ret Time	Area %	
1	23.19	0.06	
2	23.35	0.01	
3	23.60	0.01	
4	23.87	0.10	
5	24.02	0.15	exo-THC
6	24.21	0.37	(-)-∆ ⁸ -THC
7	24.64	99.01	(-)-∆ ⁹ -THC
8	25.45	0.24	
9	25.69	0.04	
10	26.06	0.01	
11	27.41	0.01	

Residual Solvent Analysis by GC/FID Headspace



Column: Temp Program: Carrier Gas: Flow Rate: Detector Heater Temp: Injector: HS Oven Temp: Vial Equilibration:		DB-ALC1 30 m x 0.53 mm, 3 µm film thickness 40°C hold 12 min to 220°C at 40°C/min hold 5.5 min Helium 2.0 mL/min 250°C Headspace Sampler 60°C 10 minutes	
Acquired	•	lanuary 31 20	120
Acquired	•	Junuary 51, 20	20
Peak	Compound	Area	Weight %
1	Hexanes	4799.00	1.30
2	Ethyl acetate	12.19	0.04
3	NMP	NA	NA
Total			1.34



GC/MS



Stability

Short term stability studies have been performed in multiple storage conditions for a period of up to four weeks. Short term data is utilized 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 stability findings for this product is listed below.

Storage Condition	Mean Kinetic Temperature (MKT)	Time Period/Result	
Freezer	-15°C		
Refrigerator	4°C	No decrease in purity was noted after	
Room Temperature	21°C	four weeks.	
40°C	40°C		
<i>Transport/Shipping:</i> 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 for a related product (T-003, $(-)-\Delta^9$ -THC) 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	June 01, 2020	Initial version.