

Certified Reference Material - Certificate of Analysis

Acety	/l fentanyl, I	Primary Measurement Stan	dard	Cerilliant Quality
-	N-phenyl-N-[1-(2	<i>2-phenylethyl)-4-piperidinyl]-acetamide</i>		ISO 17034
Product No.:	A-109-1ML			ISO/IEC 17025
Lot No.:	FC12271801			ISO 13485
Description of CRM:	Acetyl fentany	l in Methanol (Solution)		150 14001
Expiration Date:	January 2023	See Section "Stability Assessme	ent".	130 14001
Storage:	Store unopene	ed in freezer (-10 °C to -25 °C).		ISO 9001
Shipping:	Ambient.	See Section "Stability Assessment".	0 ($\sim_N \sim$
Chemical formula:	$C_{21}H_{26}N_2O$			Ĵ 🔶
CAS No.:	3258-84-2			
Regulatory:	USDEA schedu	ule I/9821 Canadian TK # 61-1018		\sim

Analyte	Certified Concentration \pm associated uncertainty U, $u=k*u$ (k=2)
Acetyl fentanyl	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 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.



January 17, 2019

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 calcuated based on: the actual mass; Mass balance purity factor of the analyte(s); measured mass of the solution; and the density of the pure diluent at 20°C.
- Fill volume is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- Concentration is verified against an independently prepared calibration solution gravimetrically prepared.
- Additional certification information available upon request.

Solution Standard Verification

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

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

Standard Solution	Assay Parameters	Calibration Curve	
Analysis Method:	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 (30:70)	Linearity (r) :	1.000
Flow Rate:	1.5 mL/min		
Wavelength:	210 nm		
	Verified Concentration	on (mg/mL) 9	%RSD - Homogeneity

		verified Concentration (mg/mL)	%KSD - Homogeneity	
Standard Solution	Lot Number	Actual Results	Actual Results	
New Lot	FC12271801	1.002	0.9	
Previous Lot	FC08011601	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:	Acetyl fentanyl FC10011801	Chemical Form CAS Number: Molecular Weig	ula: C21H26N2O 3258-84-2 322.44
	Material Charact	erization Summary	
Analytical Test		Method	Results
Primary Chromatographic Purity by GC/FID Analysis		SP10-0101	99.4% ¹
Secondary Chromatographic Purity by HPLC/UV Analysis		SP10-0102	99.6% ²
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 ³	0.27%
Residual Water Analysis by Karl Fischer Coulometry		AM1346 ³	Not Detected
Inorganic Content by Microash Analysis		SP10-0135	< 0.2%
Mass Balance Purity Fact	or		99.09%

¹ 0.02% 4-ANPP detected by GC/FID analysis.

² No 4-ANPP 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



Column:	DB-5ms	s, 30 m x 0.53 mm ID,	,
	1.5 µm	film thickness	
Temp Progr	am: 40°C to	200°C at 40°C/min	
	200°C t	to 300°C at 5°C/min	
	hold 16	min	
Injector Ter	np: Cool-on	-Column	
Detector Te	mp: 325°C		
Sample Nan	1e: FC1001	1801	
Acquired:	Noveml	per 30, 2018	
Реак #	Ret Time	Area %	
Реак # 1	6.47	Area % 0.00	
Реак # 1 2	6.47 7.67	Area % 0.00 0.07	
Peak # 1 2 3	6.47 7.67 15.32	Area % 0.00 0.07 0.02	
Реак # 1 2 3 4	6.47 7.67 15.32 15.95	Area % 0.00 0.07 0.02 0.00	
Реак # 1 2 3 4 5	Ret Time 6.47 7.67 15.32 15.95 17.06	Area % 0.00 0.07 0.02 0.00 0.38	
Реак # 1 2 3 4 5 6	Ret Time 6.47 7.67 15.32 15.95 17.06 18.32	Area % 0.00 0.07 0.02 0.00 0.38 99.36	

Peak #3 has been identified as 4-ANPP

20.95

22.00

0.00

0.16

8

9



Column:	Ascentis Ex	xpress Ph	enyl-Hexyl,
	2.7 µm, 3.	0 x 100 r	nm
Mobile Phase	e: A: Acetoni	trile	
	B: 0.1% P	hosphoric	acid in Water
Gradient:	Time (min)	% A	% B
	0.0	10	90
	8.0	60	40
	9.0	60	40
	9.1	10	90
Flow Rate:	0.7 mL/mi	n	
Wavelength:	210 nm		
Sample Nam	e: FC1001180)1	
Acquired:	November	29, 2018	1
Peak #	Ret Time	Area %	
1	3.42	0.07	
2	4.52	99.57	
3	4.97	0.08	
4	5.53	0.17	
5	5.89	0.10	

HPLC/UV

DB-ALC1 30 m x 0.53 mm, Column: MA-126 FC10011801 11.01mg.E Norm. 500 -3 µm film thickness **Temp Program:** 40°C hold 12 min to 220°C at 40°C/min hold 5.5 min 400 **Carrier Gas:** Helium Flow Rate: 2.0 mL/min **Detector Heater Temp:** 250°C 300 Injector: Headspace Sampler HS Oven Temp: 60°C Vial Equilibration: 10 minutes 200 FC10011801 Sample Name: 100 Acquired: November 29, 2018 Peak Compound Weight % Area 1 Methanol 34.27 0.27 17.0 2 NMP NA NA Total 0.27

Residual Solvent Analysis by GC/FID Headspace

e **g**erilli:

¹H NMR

Q11291802_PROTON-7.jdf Signature: File is not signed, printed by sgi RMA-126_FC10011801

	Solvent:	Chloroform-D
nt)		

Instrument:

JEOL ECS 400



LC/MS



Stability

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

Short Term Stability: A summary of accelerated stability findings for a related product (A-110, Acetyl fentanyl ${}^{13}C_6$) 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 52 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	January 17, 2019	Initial version.



Certified Reference Material - Certificate of Analysis

Acetyl fentanyl-¹³C₆, Primary Measurement Standard

	N-Phenyl-N-[1-(2-phenylethyl)-4-piperidinyl] acetamide- $^{13}C_6$	Cerilliant Quality
Product No.:	A-171-1ML	
Lot No.:	FC01041901	ISO 17034
Description of CRM:	Acetyl fentanyl- $^{13}C_6$ in Methanol (Solution)	ISO/IEC 17025
Retest Date:	October 2021 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:	$C_{15}^{13}C_{6}H_{26}N_{2}O$	
Regulatory:	USDEA Schedule I	

Analyte		Certified Concentration \pm associated uncertainty U, $u=k*u$ (k=2)	
Acetyl fentany	I- ¹³ C ₆	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 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	ive applications	
Instructions for handling and correct use:	Concentration is of solvents and reside Users should quare laboratory practice 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 acceedited by the US accreditation authority ANAB as acceeding an accordance with ISO 17034 sting laboratory AT-1352 according to ISO/IEC 17025.	



Darron Ellsworth, Quality Assurance Manager

December 01, 2020

Issue Date

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Packaging:	2 mL amber USP Type 1 glass ampoule containing not less than 1 mL of certified solution. Ampoules are overfilled to ensure a minimum of 1 mL volume can be transferred when using a 1mL Class A volumetric pipette.
Details on starting materials:	Each raw material utilized has been identified and thoroughly characterized through the use of multiple analytical techniques and is assigned a Mass Balance Purity Factor. Spectral data is provided on subsequent pages of this CoA.
Certificate of Origin:	Cerilliant Corporation certifies no material of animal origin (BSE/TSE) was used in the preparation of this product. This material was manufactured in the USA.

Associated uncertainty:

The uncertainty has been calculated by statistical analysis of all aspects of our production system and incorporated uncertainty of the mass balance purity factor, material density, balance, weighing technique, and homogeneity. Uncertainty components of the gravimetrically prepared Primary Standard concentration are shown in the figure below. Uncertainty is expressed as an expanded uncertainty in accordance with ISO 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 calcuated based on: the actual mass; Mass balance purity factor of the analyte(s); measured mass of the solution; and the density of the pure diluent at 20°C.
- Fill volume is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- Concentration is verified against an independently prepared calibration solution gravimetrically prepared.
- Additional certification information available upon request.

Solution Standard Verification

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

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: Mobile Phase:	Ascentis Express C: Acetonitrile:0.1% P (25:75)	18, 2.7 µm, 3.0 x 50 mm Phosphoric acid in Water	Number of Linearity (r	Points:):	4 1.000
Flow Rate:	1.5 mL/min				
Wavelength:	210 nm				
		Verified Concentration	n (mg/mL)	%	RSD - Homogeneity
Chausdaud					

Standard Solution	Lot Number	Actual Results	Actual Results
New Lot	FC01041901	0.994	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:	Acetyl fentanyl- ¹³ C ₆ FN07251301	Chemical Form Molecular Weig	iula: C ₁₅ ght: 328	¹³ C ₆ H ₂₆ N ₂ O 5.41
	Material Characte	erization Summary		
Analytical Test		Method	Res	ults
Primary Chromatographic	c Purity by GC/FID Analysis	SP10-0101	99.7%	
Secondary Chromatograp Analysis	hic Purity by HPLPC/UV	SP10-0102	99.	53%
Identity by LC/MS Analys	sis	SP10-0107	Consistent w	ith Structure
			0.00% 13	C ₀ vs ¹³ C ₆
		SP10-0107	0.00% ¹³ C ₀	0.04% ¹³ C ₄
Isotopic Purity and Distril	bution by LC/MS SIM Analysis		0.00% ¹³ C ₁	3.60% ¹³ C ₅
			0.00% ¹³ C ₂	96.36% ¹³ C ₆
			0.00% ¹³ C ₃	
Identity by ¹ H-NMR Analy	ysis	USP <761>, SP10-0116	Consistent w	ith Structure
Residual Solvent Analysis	s by GC/FID Headspace	AM1087 ¹	None Detected	
Residual Water Analysis I	by Karl Fischer Coulometry	AM1346 ¹	Below Quantitation Limit	
Inorganic Content by Mic	roash Analysis	SP10-0135	< 0.2%	
Mass Balance Purity Factor			99.0	58%

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	ms, 30 m x 0.53 mm ID,
	1.5 µ	m film thickness
Temp Prog	ram: 40°C	to 200°C at 40°C/min
	200°	C to 300°C at 5°C/min
	hold	16 min
Injector Te	emp: Cool-	on-Column
Detector T	emp: 325°	C
Sample Na	me: FN07	251301
Acquired:	May 1	15, 2017
Peak #	Ret Time	Area %
1	6.90	0.01
2	8.19	0.11
3	8.63	0.02

0.09

99.75

0.02

0.01

0.23

0.03

0.01

0.01

16.12

19.19

HPLC/UV



Column:	Ascentis E	xpress C1	8, 2.7	ım,
	3.0 x 50 n	ım		
Mobile Phas	se: A: Acetoni	trile		
	B: 0.1% P	hosphoric	acid in	Water
Gradient:	Time (min) % A	% B	_
	0.0	10	90	-
	3.0	50	50	
	4.0	50	50	
	4.1	10	90	
Flow Rate:	1.0 mL/mi	n		
Wavelength	210 nm			
Sample Nan Acquired:	ne: FN072513 May 31 2	01		
Acquircui	110y 51, 2	517		
Peak #	Ret Time	Area %		
1	1.27	0.02		
2	1.33	0.08		
3	1.96	99.53		
4	2.23	0.04		
5	2.30	0.03		

6

7

8

9

10

11

2.34

2.51

2.59

2.63

2.80 2.94

4

5



Residual Solvent Analysis by GC/FID Headspace



Cerilliant Corporation, 811 Paloma Drive, Suite A Round Rock, e 7 of 10 TX 78665, USA, Tel: 800-848-7837 / 512-238-9974

			_
LC	Γ	М	S



Isotopic Purity by LC/MS SIM



Stability

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

Short Term Stability: A summary of accelerated stability findings for 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 21 months has been established for this product 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	January 24, 2019	Initial version.
01	January 24, 2020	Revised Retest Date from March 2020 to January 2021.
02	December 01, 2020	Revised Retest Date from January 2021 to October 2021.



Certified Reference Material - Certificate of Analysis

Acryl	Cerilliant Quality	
N-ph	enyl-N-[1-(2-phenylethyl)-4-piperidinyl]-2-propenamide HCl;	ISO 17034
	Acryloyl fentanyl	ISO/IEC 17025
Product No.:	A-172-1ML	100 10405
Lot No.:	FC01071901	150 13485
Description of CRM:	Acryl fentanyl HCl in Methanol (Solution)	ISO 14001
	Nominal concentration is adjusted for HCl content.	ISO 9001
Retest Date:	September 2021 See Section "Stability Assessment".	
Storage:	Store unopened in freezer (-10 °C to -25 °C).	
Shipping:	Ambient. See Section "Stability Assessment".	~ <u>N</u> ~
Chemical formula:	$C_{22}H_{26}N_2O \bullet HCI$ $H_2C \downarrow I_N$	
CAS No.:	79279-03-1	• HCI
Regulatory:	USDEA Schedule I	

Analyte		Certified Concentration \pm associated uncertainty U, $u=k*u$ (k=2)	
Acryl fentar	nyl	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 valu characterized star page 2.	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 quantitat	ive applications	
Instructions for handling and correct use:	Concentration is of solvents and reside Users should quare laboratory practice concentration. Ea Nominal concentration before use.	corrected for chromatographic purity, residual water, residual dual inorganics. No adjustment required before use. ntitatively transfer desired volume using established good ses to spike into matrix or to dilute to the desired ch ampoule is intended for one-time use. ation is adjusted for HCl content. No adjustment required	
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 referer and registered test	accredited by the US accreditation authority ANAB as needed and the second accreditation authority ANAB as needec and the store according to ISO/IEC 17025.	



Darron Ellsworth, Quality Assurance Manager

September 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.
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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.

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Concentration accuracy and within- and between-bottle homogeneity areanalytically 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
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 (30:70)	Linearity (r) :	1.000
Flow Rate:	1.5 mL/min		
Wavelength:	210 nm		
	Verified Concentration	(mg/mL) %	RSD - Homogeneity

		Vermed concentration (mg/me)	/oksb = nonogeneity
Standard Solution	Lot Number	Actual Results	Actual Results
New Lot	FC01071901	1.009	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:	Acryl fentanyl HCl	Molecular Weig	ght (ba	se): 334	.45
Material Lot:	FC10011803	Molecular Weig	ght (sal	l t): 370	.92
Chemical Formula:	C ₂₂ H ₂₆ N ₂ O•HCl	Salt Adjustmer	nt:	1.10)9
CAS Number:	79279-03-1				
	Material Characte	erization Summary			
Analytical Test		Method	Results		
Primary Chromatographic	Purity by HPLC/UV Analysis	SP10-0102		99.3% ¹	
Secondary Chromatograph	nic Purity by LC/MS Analysis	SP10-0107		99.5%	
Identity by LC/MS Analysis	S	SP10-0107	Consistent with Structure		
Identity by ¹ H-NMR Analysis		USP <761>, SP10-0116	Con	Consistent with Structure	
Residual Solvent Analysis by GC/FID Headspace		AM1087 ²		0.13%	
Residual Water Analysis by Karl Fischer Coulometry		AM1346 ²	Not Detected		
Inorganic Content by Microash Analysis		SP10-0135	< 0.2%		
				Calculated	Analyzed
Elemental Analysis		Outsourced	С	71.24%	71.31%
			н	7.34%	7.32%
			N	7.55%	7.66%
Mass Balance Purity Factor				99.21%	

¹ No 4-ANPP or Fentanyl 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 C1	L8, 2.7 µ	ım	
	3.0 x 100) mm			
Mobile Phas	Se: A: Aceto	nitrile			
	B: 0.1%	Phosphoric	: acid in	Water	
Gradient:	Time (mi	n) %A	% B	_	
	0.0	10	90	-	
	8.0	70	30		
	10.0	70	30		
	10.1	10	90		
Flow Rate:	0.7 mL/n	nin			
Wavelength	210 nm	210 nm			
_					
Sample Nar	ne: FC10011	803			
Acquired:	Decembe	er 04, 2018	3		
•					
Peak #	Ret Time	Area %			
1	2.30	0.02			
2	3.28	0.01			
3	3.31	0.01			
4	3.61	99.39			
5	4.11	0.14			
6	4.29	0.08			
7	4.42	0.34			

4.60

Residual Solvent Analysis by GC/FID Headspace



Column:		DB-ALC1 30 m	x 0.53 mm,	
		3 µm film thick	iness	
Temp Pr	ogram:	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	1	Headspace Sampler		
HS Oven	Temp:	60°C		
Vial Equilibration:		10 minutes		
Sample I	Name:	FC10011803		
	l:	December 06, 2018		
		December 007	2010	
Peak	Compound	Area	Weight %	
1	Methanol	13.20	0.13	
2	NMP	NA	NA	
Total			0.13	

0.01

8







Stability

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

Short Term Stability: A summary of accelerated stability findings for 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 20 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.

Revision No.	Date	Reason for Revision
00	January 28, 2019	Initial version.
01	January 24, 2020	Revised Retest Date from March 2020 to December 2020.
02	September 29, 2020	Revised Retest Date from December 2020 to September 2021.

COA Revision History



Certified Reference Material - Certificate of Analysis

Acryl	fentanyl- ¹³ C ₆ , Primary Measurement Standard	Cerilliant Quality
N-p	henyl-N-[1-(2-phenylethyl)-4-[piperidinyl]-2-propenamide- ¹³ C ₆ HCl	ISO 17034
Product No.:	A-173-1ML	ISO/IEC 17025
Lot No.:	FC01081901	130/120 17023
Description of CRM:	Acryl fentanyl- $^{13}C_6$ HCl in Methanol (Solution)	ISO 13485
	Nominal concentration is adjusted for HCl content.	ISO 14001
Retest Date:	September 2021 See Section "Stability Assessment".	ISO 9001
Storage:	Store unopened in freezer (-10 °C to -25 °C).	
Shipping:	Ambient. See Section "Stability Assessment".	• HCI
Chemical formula:	$C_{16}^{13}C_6H_{26}N_2O \bullet HCI$	
Regulatory:	USDEA Schedule I	

Analyte		Certified Concentration \pm associated uncertainty U, $u=k*u$ (k=2)	
Acryl fentanyl	- ¹³ C ₆	1.000 ± 0.006 mg/mL	
Metrological traceability:	Traceable to the S chain of comparis	SI 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 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. For MS Applications, 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 ce material producer AR-1353 in accordance with ISO 17034 sting laboratory AT-1352 according to ISO/IEC 17025.	



Darron Ellsworth, Quality Assurance Manager

September 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 calcuated based on: the actual mass; Mass balance purity factor of the analyte(s); measured mass of the solution; and the density of the pure diluent at 20°C.
- Fill volume is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- Concentration is verified against an independently prepared calibration solution gravimetrically prepared.
- Additional certification information available upon request.

Solution Standard Verification

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

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 (30:70)	Linearity (r) :	1.000	
Flow Rate:	1.5 mL/min			
Wavelength:	210 nm			
	Verified Concentratic	(ma/ml) %	PSD - Homogeneity	

		vermed Concentration (mg/mL)	%KSD - Homogeneity
Standard Solution	Lot Number	Actual Results	Actual Results
New Lot	FC01081901	1.007	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 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:	Acryl fentanyl- ${}^{13}C_6$ HCl FC10101803 $C_{16}{}^{13}C_6H_{26}N_2O \bullet$ HCl	Molecular Weig Molecular Weig Salt Adjustmer	ght (base): ght (salt): nt:	340.41 376.87 1.107					
Material Characterization Summary									
Analytical Test		Method	Results						
Primary Chromatographic	Purity by HPLC/UV Analysis	SP10-0102	99.3% ¹						
Secondary Chromatographic Purity by LC/MS Analysis		SP10-0107	> 99.9%						
Identity by LC/MS Analysis		SP10-0107	Consistent with Structure						
			0.01% 13	C ₀ vs ¹³ C ₆					
			0.01% ¹³ C ₀	0.02% ¹³ C ₄					
Isotopic Purity and Distribution by LC/MS SIM Analysis		SP10-0107	0.00% ¹³ C ₁	2.00% ¹³ C ₅					
			0.00% ¹³ C ₂	97.97% ¹³ C ₆					
			0.00% ¹³ C ₃						
Identity by ¹ H-NMR Analysis		USP <761>, SP10-0116	Consistent with Structure						
Residual Solvent Analysis by GC/FID Headspace		AM1087 ²	None Detected						
Residual Water Analysis by Karl Fischer Coulometry		AM1346 ²	Not Detected						
Inorganic Content by Microash Analysis		SP10-0135	< 0.2%						
Mass Balance Purity Factor			99.30%						

¹ 0.32% 4-ANPP detected by HPLC/UV analysis; no Fentanyl 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 4-ANPP



Residual Solvent Analysis by GC/FID Headspace




Isotopic Purity by LC/MS SIM



Stability

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

Short Term Stability: A summary of accelerated stability findings for a related product (A-140-0.5ML, Acryl fentanyl 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 20 months has been established for a related product (A-172-1ML, Acryl fentanyl HCl) 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	January 29, 2019	Initial version.
01	January 24, 2020	Revised Retest Date of March 2020 to December 2020.
02	September 29, 2020	Revised Retest Date of December 2020 to September 2021.



Certified Reference Material - Certificate of Analysis

	4-ANPP, Primary Measurement Standard	Cerilliant Quality
	N-Phenyl-1-(2-phenethyl)-4-piperidinamine	ISO 17034
Product No.:	A-174-1ML	ISO/IEC 17025
Lot No.:	FC01141902	150 12495
Description of CRM:	4-ANPP in Methanol (Solution)	130 13465
Retest Date:	December 2021 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 ₁₉ H ₂₄ N ₂	N'
CAS No.:	21409-26-7 HŅ	
Regulatory:	USDEA Schedule II	

Analyte	Certified Concentration ± associated uncertainty U, u=k*u (k=2)		
4-ANPP	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	Concentration is corrected for chromatographic purity, residual water, residual
handling and correct use:	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.
handling and correct use: Health and safety information:	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.



Darron Ellsworth, Quality Assurance Manager

December 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 calcuated based on: the actual mass; Mass balance purity factor of the analyte(s); measured mass of the solution; and the density of the pure diluent at 20°C.
- Fill volume is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- Concentration is verified against an independently prepared calibration solution gravimetrically prepared.
- Additional certification information available upon request.

Solution Standard Verification

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

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 (30:70)	Linearity (r) :	1.000
Flow Rate:	1.5 mL/min		
Wavelength:	210 nm		
	Varified Concentratio		

		verified Concentration (mg/mL)	%RSD - Homogeneity
Standard Solution	Lot Number	Actual Results	Actual Results
New Lot	FC01141902	0.996	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:	4-ANPP FC10041801	Chemical Form CAS Number: Molecular Weig	nula: C ₁₉ H ₂₄ N ₂ 21409-26-7 ght: 280.41
	Material Characte	erization Summary	
Analytical Test		Method	Results
Primary Chromatographi	c Purity by HPLC/UV Analysis	SP10-0102	99.7%
Secondary Chromatographic Purity by GC/FID Analysis		SP10-0101	99.7%
Identity by LC/MS Analysis		SP10-0107	Consistent with Structure
Identity by ¹ H-NMR Anal	ysis	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	Not Detected
Inorganic Content by Microash Analysis		SP10-0135	< 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

HPLC/UV



Column:	Ascentis	Express Ph	enyl-He	exyl,
Mobile Pha	2.7μm, Δ:Δcoto	3.U X 100 ľ	nm	
MODILE FILAS	B: 0.1%	Phosphoric	acid in	Water
Gradient:	Time (m	in) %A	% B	mater
	0.0	5	95	-
	8.0	80	20	
	10.0	80	20	
	10.1	5	95	
Flow Rate:	0.7 mL/	min		
Wavelength	1: 210 nm			
Sample Nar	ne: FC10042	1801		
Acquired:	Decemb	er 13, 2018		
Peak #	Ret Time	Area %		
1	3.07	0.01		
2	3.16	0.01		
3	3.62	0.02		
4	3.71	0.01		
5	3.82	0.28		
6	3.97	99.48		
7	4.31	0.11		
8	4.62	0.02		
9	4.98	0.01		
10	6.06	0.02		
11	6.10	0.02		

GC/FID



Column:		DB-35 1.0 µr	ms, 30 m x 0.53 mm ID n film thickness	,
-	Temp Prog	ram: 40°C 200°C hold 1	to 200°C at 40°C/min to 280°C at 5°C/min 8 min	
	Injector Te	mp: Cool-c	on-Column	
Detector Temp:		emp: 325°C	325°C	
:	Sample Na	me: FC100	41801	
4	Acquired:	Decen	nber 11, 2018	
_	Peak #	Ret Time	Area %	
	1	6.51	0.00	
	2	6.88	0.00	
	3	15.89	0.26	
	4	16.70	99.68	
	5	17.08	0.04	
	6	18.89	0.00	
	7	25.77	0.00	

Residual Solvent Analysis by GC/FID Headspace



¹H NMR

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X : parts per Million : 1H	

Instrument: JEOL ECS 400 Solvent: Chloroform-D



Stability

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

Short Term Stability: A summary of accelerated stability findings for 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 22 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 06, 2019	Initial version.
01	01 March 15, 2020	Updated Retest Date of April 2020 to February 2021.
01		Added Long Term Stability.
02	December 29, 2020	Updated Retest Date of February 2021 to December 2021.



Certified Reference Material - Certificate of Analysis

4-A	NPP- ¹³ C ₆ , Primary Measurement Standard	Cerilliant Quality
	N-Phenyl-1-(2-phenethyl)-4-piperidinamine- ¹³ C ₆	ISO 17034
Product No.:	A-175-1ML	ISO/IEC 17025
Lot No.:	FC01081902	150 13485
Description of CRM:	4-ANPP- ¹³ C ₆ in Methanol (Solution)	150 10403
Retest Date:	October 2021 See Section "Stability Assessment".	150 14001
Storage:	Store unopened in freezer (-10 °C to -25 °C).	ISO 9001
Shipping:	Ambient. See Section "Stability Assessment".	
Chemical formula:	¹³ C ₆ C ₁₃ H ₂₄ N ₂	
CAS No.:	NA J*	J
Regulatory:	USDEA Schedule II	

Analyte		Certified Concentration \pm associated uncertainty U, u=k*u (k=2)	
4-ANPP- ¹³ C	6	1.000 ± 0.006 mg/mL	
Metrological traceability:	Traceable to the unbroken chain of page 2.	SI and higher order standards from NIST through an of comparisons. See "Details on metrological traceability" on	
Measurement method:	The certified value characterized state page 2.	ue is calculated from high precision weighing of thoroughly arting 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 sequence		
Health and safety information:	Danger. Please r the nature of any	efer to the Safety Data Sheet for detailed information about y 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.		
	A		



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October 26, 2020

Darron Ellsworth, Quality Assurance Manager

Issue Date

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Packaging:	2 mL amber USP Type 1 glass ampoule containing not less than 1 mL of certified solution. Ampoules are overfilled to ensure a minimum of 1 mL volume can be transferred when using a 1mL Class A volumetric pipette.
Details on starting materials:	Each raw material utilized has been identified and thoroughly characterized through the use of multiple analytical techniques and is assigned a Mass Balance Purity Factor. Spectral data is provided on subsequent pages of this CoA.
Certificate of Origin:	Cerilliant Corporation certifies no material of animal origin (BSE/TSE) was used in the preparation of this product. This material was manufactured in the USA.

Associated uncertainty:

The uncertainty has been calculated by statistical analysis of all aspects of our production system and incorporated uncertainty of the mass balance purity factor, material density, balance, weighing technique, and homogeneity. Uncertainty components of the gravimetrically prepared Primary Standard concentration are shown in the figure below. Uncertainty is expressed as an expanded uncertainty in accordance with ISO 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 calcuated based on: the actual mass; Mass balance purity factor of the analyte(s); measured mass of the solution; and the density of the pure diluent at 20°C.
- Fill volume is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- Concentration is verified against an independently prepared calibration solution gravimetrically prepared.
- Additional certification information available upon request.

Solution Standard Verification

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

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 Regres		Linear Regression	
Column:	Ascentis Express C1	Number of Points: 4		4	
Mobile Phase:	Acetonitrile:0.1% P (25:75)	Linearity (r):	1.000	
Flow Rate:	1.5 mL/min				
Wavelength:	210 nm				
		Verified Concentration	n (mg/mL)	%	RSD - Homogeneity
Standard Solution	Lot Number	Actual Result	ts		Actual Results
New Lot	FC01081902	1.006			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:4-ANPP-13C6Material Lot:FC10171801	Chemical Form CAS Number: Molecular Weig	nula: ¹³ C ₆ NA ght: 286	.36	
Material Charac	terization Summary			
Analytical Test	Method	Re	sults	
Primary Chromatographic Purity by HPLC/UV Analysis	SP10-0102	99	.7%	
Secondary Chromatographic Purity by GC/FID Analysis	SP10-0101	99	.8%	
Identity by LC/MS Analysis	SP10-0107	Consistent v	with Structure	
		0.01% ¹³ C ₀ vs ¹³ C ₆		
	SP10-0107	0.01% ¹³ C ₀	0.04% ¹³ C ₄	
Isotopic Purity and Distribution by LC/MS SIM Analysis		0.00% ¹³ C ₁	2.57% ¹³ C ₅	
		0.00% ¹³ C ₂	97.38% ¹³ C ₆	
		0.01% ¹³ C ₃		
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	Not Detected		
Inorganic Content by Microash Analysis	SP10-0135	< 0.2%		
Mass Balance Purity Factor		99.	70%	

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





LC/MS

Column: Ascentis Express C18, 2.7 µ 3.0 x 50 mm			m, Flow Rat Scan Ra	te:	0.4 mL/min 100-1200 amu	
Mobile Phase:	A: 0.1% Fo B: Acetoniti	rmic aci rile	d in Wat	er Ionizatio Instrum	Ionization:	Electrospray, Positive Ion Waters XEVO G2 OTOF
Gradient:	Time (min)	% A	% B	Acquired	1:	December 17, 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			
RMA-156 FC101718	01			4-ANPP-13C6		Cone Voltage: 15.0000000
W12171827 686 (2 565	(088·680)					1. TOF MS ES+
1111021 000 (2.000						
	287.2213					8.90e5
	Theo	oretical [[М + Н] [.]	: 287.2219		
144.1140	Four	nd [M +	H]+• 28	7 2213		
	1001		11] . 20	.2215		
8						
-	288 22/10					
183.1591 28	200.22+3			207 1001		
	0.2100			687.4324		
0						•_•••••

Isotopic Purity by LC/MS SIM



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

Short Term Stability: A summary of accelerated stability findings for a related product (A-139-0.5ML, 4-ANPP) 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 21 months has been established for this product 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	January 25, 2019	Initial version.
01	January 24, 2020	Updated Retest Date of March 2020 to January 2021.
02	October 26, 2020	Updated Retest Date of January 2021 to October 2021.



Certified Reference Material - Certificate of Analysis

Butyryl fentanyl, Primary Measurement Standard

N-Phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]butanamide; Butyryl fentanyl (BF, NIH-10486); Fentanyl butanamide analogue

ISO 17034 ISO/IEC 17025 ISO 13485 ISO 14001

Dreduct No.				
Product No.:	D-003-IML		150 14	4001
Lot No.:	FC01031904		130 1-	1001
Description of CRM:	Butyryl fentanyl in Methanol (Solution)		ISO 9	001
Retest Date:	November 2021 See Section "Stability Assessment"			
Storage:	Store unopened in freezer (-10 °C to -25 °C).	0		
Shipping:	Ambient. See Section "Stability Assessment".			
Chemical formula:	$C_{23}H_{30}N_2O$	H ₃ C	N	
CAS No.:	1169-70-6	(
Regulatory:	USDEA Schedule I	Į		
			· /	

Analyte		Certified Concentration \pm associated uncertainty U, $u=k*u$ (k=2)	
Butyryl fenta	inyl	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 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 registered referent and registered test	accredited by the US accreditation authority ANAB as nee material producer AR-1353 in accordance with ISO 17034 sting laboratory AT-1352 according to ISO/IEC 17025.	



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December 14, 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 calcuated based on: the actual mass; Mass balance purity factor of the analyte(s); measured mass of the solution; and the density of the pure diluent at 20°C.
- Fill volume is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- Concentration is verified against an independently prepared calibration solution gravimetrically prepared.
- Additional certification information available upon request.

Solution Standard Verification

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

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

Standard Solution Assay Parameters			Calibration	Curve	
Analysis Method:	HPLC/UV		Calibration Curve: Linear		Linear Regression
Column:	Ascentis Express C18, 2.7 µm, 3.0 x 100 mm		nm Number of Points: 4		4
Mobile Phase:	Acetonitrile:0.1% Phosphoric acid in Water (35:65)		Linearity (r):	1.000
Flow Rate:	1.5 mL/min				
Wavelength:	210 nm				
		Verified Concentration	n (mg/mL)	%F	RSD - Homogeneity

			•
Standard Solution	Lot Number	Actual Results	Actual Results
New Lot	FC01031904	1.001	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:	Butyryl fentanyl FC12111801	Chemical Form CAS Number: Molecular Weig	Iula: C ₂₃ H ₃₀ N ₂ O 1169-70-6 ght: 350.50
	Material Characte	erization Summary	
Analytical Test		Method	Results
Primary Chromatographic Purity by HPLC/UV Analysis		SP10-0102	99.8%
Secondary Chromatographic Purity by GC/FID Analysis		SP10-0106	99.6%
Identity by GC/MS Analysis		SP10-0107	Consistent with Structure
Identity by ¹ H-NMR Analysis		USP <761>, SP10-0116	Consistent with Structure
Residual Solvent Analysis by GC/FID Headspace		AM1087 ¹	0.16%
Residual Water Analysis by Karl Fischer Coulometry		AM1346 ¹	Not Detected
Inorganic Content by Microash Analysis		SP10-0135	< 0.2%
Mass Balance Purity Factor			99.62%

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

FID1 A, (RIIB-102 P GC 6 2019-01-17 13-43-17 B-004-19-RIIB-102 FC 12111801D)	Column:	DB-35i 1.0 um	ms, 30 m x 0.53 mı ı film thickness	m ID,
pA .	Temp Program	m: 40°C to	o 200°C at 40°C/m to 300°C at 5°C/m	in in hold 16 min
1200-	Injector Temp	p: Cool-or	n-Column	
1000	Detector rem	p: 325°C		
800-]	Sample Name Acquired:	FC121: Januar	11801 y 17, 2019	
-1 600-1				
	Peak # R	Ret Time	Area %	
Ė m.	1	5.00	0.02	
100_	2	9.73	0.09	
] v v v v v	3	18.11	0.01	
	4	19.78	99.83	
A A A A	5	20.62	0.01	
$-\frac{1}{1}$	6	24.41	0.04	

Residual Solvent Analysis by GC/FID Headspace



HPLC/UV



Column:	Ascentis E	Express C1	8, 2.7 μ	m,
	3.0 x 100	mm		
Mobile Phase:	A: Aceton	itrile		
	B: 0.1% P	Phosphoric	acid in	Water
Gradient:	<u>Time (mir</u>	n) % A	% B	
	0.0	10	90	
	8.0	70	30	
	10.0	70	30	
	10.1	. 10	90	
Flow Rate:	0.7 mL/m	in		
Wavelength:	210 nm			
Sample Name	EC121110	01		
Acquired	PCIZIIIC	6 2010		
Acquired.	January 1	0, 2019		
Peak # Re	et Time	Area %		
1	2.71	0.01		
2	3.21	0.03		
3	3.35	0.01		
4	3.74	0.06		
5	3.85	0.01		
6	4.07	0.01		
7	4.10	0.02		
8	4.20	99.57		
9	4.46	0.06		
10	4.53	0.04		
11	4.66	0.01		
12	4.88	0.01		
13	4.98	0.02		
14	5.24	0.01		
15	5.39	0.01		
16	5.45	0.02		
17	5.53	0.01		
18	5./1	0.01		
19	5.9/	0.01		
20	6./1	0.09		







Stability

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

Short Term Stability: A summary of accelerated stability findings for 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	
Room Temperature	Temperature21°Cafter four we		
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 21 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	1
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Revision No.	Date	Reason for Revision
00	February 13, 2019	Initial version.
01	Echrupry 18 2020	Revised Retest Date from April 2020 to February 2021.
01	February 16, 2020	Added Long Term Stability section.
02	December 14, 2020	Revised Retest Date from February 2021 to November 2021.



Certified Reference Material - Certificate of Analysis

Butyryl fentanyl-¹³C₆, Primary Measurement Standard

	N -Phenyl- N -[1-(2-phenylethyl)-4-piperidinyl]butanamide- ${}^{13}C_6$	Cerilliant Quality
Product No.:	B-084-1ML	ISO 17034
Lot No.:	FC01141903	100 17004
Description of CRM:	Butyryl fentanyl- $^{13}C_6$ in Methanol (Solution)	ISO/IEC 17025
Retest Date:	November 2021 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:	$C_{17}^{13}C_6H_{30}N_2O$	
CAS No.:		5
Regulatory:	USDEA Schedule I	J
	н ¹³ С _{13С} ³³ СН Н	

Analyte		Certified Concentration ± associated uncertainty U, u=k*u (k=2)		
Butyryl fentany	/I- ¹³ C 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.	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 use:	Concentration is c solvents and resic Users should quar laboratory practic concentration. Eac 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 ce material producer AR-1353 in accordance with ISO 17034 sting laboratory AT-1352 according to ISO/IEC 17025.		



Darron Ellsworth, Quality Assurance Manager

December 14, 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 calcuated based on: the actual mass; Mass balance purity factor of the analyte(s); measured mass of the solution; and the density of the pure diluent at 20°C.
- Fill volume is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- Concentration is verified against an independently prepared calibration solution gravimetrically prepared.
- Additional certification information available upon request.

Solution Standard Verification

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

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 (35:65)	Linearity (r) :	1.000
Flow Rate:	1.5 mL/min		
Wavelength:	210 nm		
	Verified Concentratior	(mg/mL) %	RSD - Homogeneity

		vermed concentration (mg/me)	70KSD - Holliogeneity
Standard Solution	Lot Number	Actual Results	Actual Results
New Lot	FC01141903	0.998	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:	Butyryl fentanyl- ¹³ C ₆ FC10091802	Chemical Form CAS Number: Molecular Weig	nula: C ₁₇ NA ght: 356	¹³ C ₆ H ₃₀ N ₂ O 5.45	
	Material Characte	erization Summary			
Analytical Test		Method	Re	sults	
Primary Chromatographi	ic Purity by HPLC/UV Analysis	SP10-0102	99	99.1%	
Secondary Chromatogra	phic Purity by LC/MS Analysis	SP10-0107	98	.9%	
Identity by LC/MS Analy	sis	SP10-0107	Consistent v	vith Structure	
			0.01% 13	³ C ₀ vs ¹³ C ₆	
		SP10-0107	0.01% ¹³ C ₀	0.05% ¹³ C ₄	
Isotopic Purity and Distr	ibution by LC/MS SIM Analysis		0.00% ¹³ C ₁	3.07% ¹³ C ₅	
			0.00% ¹³ C ₂	96.87% ¹³ C ₆	
			0.00% ¹³ C ₃		
Identity by ¹ H-NMR Anal	ysis	USP <761>, SP10-0116	Consistent with Structure		
Residual Solvent Analysi	s by GC/FID Headspace	AM1087 ¹	0.25%		
Residual Water Analysis by Karl Fischer Coulometry		AM1346 ¹	Not Detected		
Inorganic Content by Microash Analysis		SP10-0135	< 0.2%		
Mass Balance Purity Fact	tor		98.	83%	

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 Ex	xpress C1	L8, 2.7 μr	n
Mohile Phase:	3.0 X 100 I A: Acetonii	mm trile		
Hobite i huse.	B: 0.1% Pl	hosphoric	c acid in N	Vater
Gradient:	Time (min)	% А	% B	
	0.0	10	90	
	8.0	70	30	
	10.0	70	30	
	10.1	10	90	
Flow Rate:	0.7 mL/mi	n		
Wavelength:	210 nm			
Sample Name:	FC1009180)2		
Acquired:	December	12, 2018	5	
Posk # Pot T	imo	Area %		
1 3 F	54	0.23		
2 40	00	0.25		
3 4 1	12	99.00		
	16	0.03		
5 46	56	0.05		
6 48	25	0.00		
7 40	24	0.02		
8 50		0.02		
9 52	04	0.14		
10 5 3	- 7	0.01		
10 5.5	15	0.01		
12 5.4	56	0.01		
12 5.5	8	0.02		
14 6.5	71	0.10		
15 60	5	0.01		
10		0.01		

17

7.85

0.02

Residual Solvent Analysis by GC/FID Headspace







Isotopic Purity by LC/MS SIM





Stability

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

Short Term Stability: A summary of accelerated stability findings for a related product (B-066-0.5ML, Butyryl fentanyl) 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 21 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, 2019	Initial version.
01 Fe	Echrupry 18, 2020	Revised Retest Date from April 2020 to February 2021.
	February 16, 2020	Added Long Term Stability section.
0.2	December 14, 2020	Revised Retest Date from February 2021 to November 2021.
02		Added chemical structure to first page.



Certified Reference Material - Certificate of Analysis

Cyclopropyl fentanyl, Primary Measurement Standard

N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]-cyclopropanecarboxamide HCl Cerilliant Quality

Product No.:	C-198-1ML	150 17034
Lot No.:	FC12261807	130 17004
Description of CRM:	Cyclopropyl fentanyl HCl in Methanol (Solution)	ISO/IEC 17025
	Nominal concentration is adjusted for HCl content.	ISO 13485
Retest Date:	November 2021 See Section "Stability Assessment".	ISO 14001
Storage:	Store unopened in freezer (-10 °C to -25 °C).	ISO 9001
Shipping:	Ambient. See Section "Stability Assessment".	HCI
Chemical formula:	$C_{23}H_{28}N_2O \bullet HCI$	\sim
CAS No.:	NA	
Regulatory:	USDEA Schedule I	

Analyte		Certified Concentration \pm associated uncertainty U, $u=k*u$ (k=2)		
Cyclopropyl fer	ntanyl	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 a standards from NIST through an for a standard standard the standard st		
Measurement method:	The certified value characterized star page 2.	The certified value is calculated from high precision weighing of thoroughly characterized starting material. See "Details about certification process" on bage 2.		
Intended use:	This Certified Reference Material is suitable for the in vitro identification, calibration, and quantification of the analyte(s) in analytical and R&D applications. Not suitable for human or animal consumption.			
Minimum sample size:	1 μL for quantitative applications			
Instructions for handling and correct use:	Concentration is corrected for chromatographic purity, residual solvents and residual inorganics. No adjustment required before use. Users should quantitatively transfer desired volume using established good laboratory practices to spike into matrix or to dilute to the desired concentration. Each ampoule is intended for one-time use. Nominal concentration is adjusted for HCl content. No adjustment required			
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

January 11, 2021

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 calcuated based on: the actual mass; Mass balance purity factor of the analyte(s); measured mass of the solution; and the density of the pure diluent at 20°C.
- Fill volume is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- Concentration is verified against an independently prepared calibration solution gravimetrically prepared.
- Additional certification information available upon request.

Solution Standard Verification

Concentration accuracy and within- and between-bottle homogeneity 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 C	Curve	
Analysis Method:	Calibration Curve: Linear Regression		Linear Regression	
Column:	Number of P	oints:	4	
Mobile Phase:	Acetonitrile:0.1% Phosphoric acid in Water (30:70)	Linearity (r) : 1.000		1.000
Flow Rate: 1.7 mL/min				
Wavelength:	210 nm			
	Verified Concentration	n (mg/mL)	%F	SD - Homogeneity

		······································	,
Standard Solution	Lot Number	Actual Results	Actual Results
New Lot	FC12261807	0.993	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 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:	Cyclopropyl fentanyl HCl FC10031801 $C_{23}H_{28}N_2O \bullet$ HCl	Molecular Weig Molecular Weig Salt Adjustmei	ght (ba: ght (sal nt:	se): 348 l t): 384 1.10	.48 .94)5
CAS NUMBER:		- viti C			
	Material Characte	erization Summary			
Analytical Test		Method		Results	
Primary Chromatographic	Purity by HPLC/UV Analysis	SP10-0102		99.4% ¹	
Secondary Chromatograph	nic Purity by GC/FID Analysis	SP10-0101		99.3% ¹	
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 ²	None Detected		
Residual Water Analysis by Karl Fischer Coulometry		AM1346 ²	Below Quantitation Limit		
Inorganic Content by Micr	oash Analysis	SP10-0135	< 0.2%		
				Calculated	Analyzed
Elemental Analysis		Outcoursed	С	71.76%	71.59%
Elemental Analysis		Outsourced	Н	7.59%	7.61%
			Ν	7.28%	7.45%
Mass Balance Purity Facto			99.42%		

¹ No 4-ANPP or Fentanyl detected by HPLC/UV or GC/FID.

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:	Ascenti	s Express P	henyl-He	xyl,
Mobile Pha	se: A: Ace B: 0.1	, 5.0 x 100 tonitrile % Phosphor	ric acid in	Water
Gradient:	Time (r	nin) %A	% B	
	0.0	10	90	
	8.0	70	30	
	10.0) 70	30	
	10.1	. 10	90	
Flow Rate:	0.7 mL	/min		
Wavelength	1: 210 nm	ו		
Sample Na	ne: FC1003	31801		
Acquired:	Februa	ry 11, 2019		
Peak #	Ret Time	Area %	D	
1	4.21	0.01		
2	4.36	0.11		
3	5.07	99.41		
4	5.78	0.07		
5	5.87	0.41		

GC/FID



Residual Solvent Analysis by GC/FID Headspace



¹H NMR

Instrument:	JEOL ECS 400
Solvent:	Chloroform-D



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LC/MS



Stability

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

Short Term Stability: A summary of accelerated stability findings for 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 20 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 21, 2019	Initial version.
01	April 03, 2020	Updated Retest Date from May 2020 to February 2021.
02	January 11, 2021	Revised Retest Date from February 2021 to November 2021.



Certified Reference Material - Certificate of Analysis

Cyclopropyl fentanyl-¹³C₆ , Primary Measurement Standard

N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]-cyclopropanecarboxamide-¹³C₆ HCl Cerilliant Quality

		Cerimani Quany
Product No.:	C-199-1ML	150 17024
Lot No.:	FC12261803	130 17034
Description of CRM:	Cyclopropyl fentanyl- ¹³ C ₆ HCl in Methanol (Solution)	ISO/IEC 17025
	Nominal concentration is adjusted for HCl content.	ISO 13485
Retest Date:	November 2021 See Section "Stability Assessment".	ISO 14001
Storage:	Store unopened in freezer (-10 °C to -25 °C).	ISO 9001
Shipping:	Ambient. See Section "Stability Assessment".	• HCI
Chemical formula:	$C_{17}^{13}C_{6}H_{28}N_{2}O \bullet HCI$	N
CAS No.:	NA VIEW NA	
Regulatory:	USDEA Schedule 1	

Analyte	Certified Concentration \pm associated uncertainty U, u=k*u (k=2)
Cyclopropyl fentanyl- ¹³ C 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 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. 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.



March 05, 2021

Darron Ellsworth, Quality Assurance Manager

Issue Date

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Packaging:	2 mL amber USP Type 1 glass ampoule containing not less than 1 mL of certified solution. Ampoules are overfilled to ensure a minimum of 1 mL volume can be transferred when using a 1mL Class A volumetric pipette.
Details on starting materials:	Each raw material utilized has been identified and thoroughly characterized through the use of multiple analytical techniques and is assigned a Mass Balance Purity Factor. Spectral data is provided on subsequent pages of this CoA.
Certificate of Origin:	Cerilliant Corporation certifies no material of animal origin (BSE/TSE) was used in the preparation of this product. This material was manufactured in the USA.

Associated uncertainty:

The uncertainty has been calculated by statistical analysis of all aspects of our production system and incorporated uncertainty of the mass balance purity factor, material density, balance, weighing technique, and homogeneity. Uncertainty components of the gravimetrically prepared Primary Standard concentration are shown in the figure below. Uncertainty is expressed as an expanded uncertainty in accordance with ISO 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 calcuated based on: the actual mass; Mass balance purity factor of the analyte(s); measured mass of the solution; and the density of the pure diluent at 20°C.
- Fill volume is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- Concentration is verified against an independently prepared calibration solution gravimetrically prepared.
- Additional certification information available upon request.

Solution Standard Verification

Concentration accuracy and within- and between-bottle homogeneity 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	
Column:	Ascentis Express C18, 2.7 µm, 3.0 x 100 mm		m Number of Points: 4		4	
Mobile Phase:	Acetonitrile:0.1% Pr (30:70)	nosphoric acid in Water	Linearity (r):	1.000	
Flow Rate:	1.7 mL/min					
Wavelength:	210 nm					
		Verified Concentration	n (mg/mL)	%	RSD - Homogeneity	

			5
Standard Solution	Lot Number	Actual Results	Actual Results
New Lot	FC12261803	1.003	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 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:	Cyclopropyl fentanyl- $^{13}C_6$ HClMoleculaFC10031803Molecula $C_{17}^{13}C_6H_{28}N_2O \bullet$ HClSalt AdjuNA		ar Weight (bas ar Weight (sal ustment:	se):	354. 390. 10	.44 .90 .3	
	Material Cha	aracterization	Summa	ry			
Analytical Test		Metho	d		Results		
Primary Chromatographic Analysis	Purity by HPLC/UV	SP10-01	02		99.5%		
Secondary Chromatograph Analysis	ic Purity by GC/FID	SP10-01	01		99.4%		
Identity by LC/MS Analysis	5	SP10-01	07	Consiste	ent with S	tru	cture
				0.00	% ¹³ C ₀ vs	¹³ C	-6
Isotopic Purity and Distribution by LC/MS SIM Analysis		SP10-0107		0.00% $^{13}C_0$ vs $^{13}C_3$		2.	08% ¹³ C ₅
				0.04% ¹³ C ₄		97	.88% ¹³ C ₆
Identity by ¹ H-NMR Analysis		USP <761>, SF	P10-0116	Consistent with Structure		cture	
Residual Solvent Analysis by GC/FID Headspace		AM1087	, 1	None Detected			
Residual Water Analysis by Coulometry	y Karl Fischer	AM1346	1	0.55%			
Inorganic Content by Micro	oash Analysis	SP10-01	35	< 0.2%			
					Calculat	ed	Analyzed
				С	52.24%	D	69.77%
Elemental Analysis		Outsourc	ea	Н	7.48%		7.44%
				Ν	7.17%		7.12%
Mass Balance Purity Factor					98.98%		

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





Column:	Ascent	is Express C	218, 2.7 μ	m,
	3.0 x 1	3.0 x 100 mm		
Mobile Phas	A: AC	etonitrile		
	B: 0.1	.% Phospho	ric acid in	Wate
Gradient:	Time (min) %A	% B	
	0.0) 10	90	
	8.0	70	30	
	10.	0 70	30	
	10.	1 10	90	
Flow Rate:	0.7 ml	/min		
Wavelength	1: 210 nr	n		
2				
Sample Nan	ne: FC100	31803		
Acquired:	Januar	y 22, 2019		
•				
Peak #	Ret Time	Area %		
1	3.26	0.03		
2	3.31	0.10		
3	3.34	0.12		
4	3.97	99.53		
5	4.28	0.05		
6	4.39	0.02		
7	4.51	0.06		
8	4.81	0.01		
9	5.00	0.06		

GC/FID



Column: Temp Prog Injector Te Detector T Sample Na	DB-3: 1.0 µ 1.0 µ 200°(20	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 300°C at 5°C/min hold 16 m Cool-on-Column 325°C FC10031803 January 25, 2010	
Acquireu:	Janua	iry 25, 2019	
Peak #	Ret Time	Area %	
		/	
1	11.59	0.04	
1	11.59	0.04	
2	17.13	0.14	
1	11.59	0.04	
2	17.13	0.14	
3	20.77	0.11	
1	11.59	0.04	
2	17.13	0.14	
3	20.77	0.11	
4	22.04	0.00	
1	11.59	0.04	
2	17.13	0.14	
3	20.77	0.11	
4	22.04	0.00	
5	22.69	0.02	
1	11.59	0.04	
2	17.13	0.14	
3	20.77	0.11	
4	22.04	0.00	
5	22.69	0.02	
6	23.16	99.44	
1	11.59	0.04	
2	17.13	0.14	
3	20.77	0.11	
4	22.04	0.00	
5	22.69	0.02	
6	23.16	99.44	
7	23.44	0.17	
1	11.59	0.04	
2	17.13	0.14	
3	20.77	0.11	
4	22.04	0.00	
5	22.69	0.02	
6	23.16	99.44	
7	23.44	0.17	
8	24.29	0.02	

Residual Solvent Analysis by GC/FID Headspace



⁺H NMR



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Isotopic Purity by LC/MS



Certficate Page 9 of 10

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Stability

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

Short Term Stability: A summary of accelerated stability findings for a related product (C-177-0.5ML, Cyclopropyl fentanyl 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 20 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 13, 2019	Initial version.
		Revised Retest Date from May 2020 to February 2021.
01	April 10, 2020	Added Long Term Stability Section.
02	March 05, 2021	Revised Retest Date from February 2021 to November 2021.



Certified Reference Material - Certificate of Analysis

Furanyl fentanyl, Primary Measurement Standard

N-Phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]-2-furancarboxamide HCl, Furanyl fentanyl (FU-F)

Product No.:	F-063-1ML	Cerilliant Quality
Lot No.:	FC12121801	ISO 17034
Description of CRM:	Furanyl fentanyl HCl in Methanol (Solution)	ISO/IEC 17025
	Nominal concentration is adjusted for HCl content.	ISO 13485
Retest Date:	September 2021 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:	$C_{24}H_{26}N_2O_2 \bullet HCI$ O N	-HCI
CAS No.:	101365-56-4	
Regulatory:	USDEA Schedule I/9834	

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

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 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

September 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 calcuated based on: the actual mass; Mass balance purity factor of the analyte(s); measured mass of the solution; and the density of the pure diluent at 20°C.
- Fill volume is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- Concentration is verified against an independently prepared calibration solution gravimetrically prepared.
- Additional certification information available upon request.

Solution Standard Verification

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

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: Column:	HPLC/UV Ascentis Express C18, 2.7 μm, 3.0 x 100 mm		Calibration Curve:Linear RegreeNumber of Points:4		Linear Regression 4
Mobile Phase: Flow Rate:	Acetonitrile:0.1% Phosphoric acid in Water (30:70) 1.5 mL/min		Linearity (r) : 1.000		1.000
Wavelength:	210 nm				
		Verified Concentration	n (mg/mL)	%	RSD - Homogeneity
Standard Solution	Lot Number	Actual Result	ts		Actual Results
New Lot	FC12121801	1.009			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:	Furanyl fentanyl HCl	Molecular Wei	ght (ba	se): 374	.48
Material Lot:	Material Lot: FC09271803 Molecular We		ght (sa	l t): 410	.94
Chemical Formula:	$C_{24}H_{26}N_2O_2\bullet HCI$	Salt Adjustme	nt:	1.09	97
CAS Number:	101365-56-4				
	Material Characte	erization Summary			
Analytical Test		Method	Results		
Primary Chromatographic	Purity by HPLC/UV Analysis	SP10-0102	99.4% ¹		
Secondary Chromatograph	nic Purity by LC/MS Analysis	SP10-0107	99.6%		
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 ²	1.27%		
Residual Water Analysis by Karl Fischer Coulometry		AM1346 ²	Below Quantitation Limit		
Inorganic Content by Microash Analysis		SP10-0135	< 0.2%		
				Calculated	Analyzed
Elemental Analysis		Outcoursed	С	70.15%	69.48%
		Outsourceu	Н	6.62%	6.89%
			Ν	6.82%	7.02%
Mass Balance Purity Factor 98.11%					

 $^{\rm 1}$ 0.20% 4-ANPP 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 I	Express C	18, 2.7 µ	ım,
	3.0 x 100	mm		
Mobile Pha	se: A: Aceton	itrile		
	B: 0.1% I	Phosphoric	c acid in	Water
Gradient:	Time (mir	n) % A	% B	
	0.0	10	90	
	8.0	70	30	
	10.0	70	30	
	10.1	10	90	
Flow Rate:	0.7 mL/m	in		
Wavelengtl	h: 210 nm			
Sample Na	me: FC092718	303		
Acquired:	Novembe	r 12, 2018	3	
Peak #	Ret Time	Area %		
1	3.74	0.20		
2	3.88	0.06		
3	4.36	99.38		
4	4.62	0.06		
5	5.16	0.05		
6	5.22	0.02		
7	5.34	0.20		
8	5.72	0.03		

Peak 1 has been identified as 4-ANPP

Residual Solvent Analysis by GC/FID Headspace





LC/MS



Stability

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

Short Term Stability: A summary of accelerated stability findings for 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 20 months has been established for this product 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.

Revision No.	Date	Reason for Revision
00	January 15, 2019	Initial version.
01	January 30, 2020	Revised Retest Date from March 2020 to December 2020.
02	September 28, 2020	Revised Retest Date from December 2020 to September 2021.

COA Revision History



Certified Reference Material - Certificate of Analysis

Furanyl fentanyl-¹³C₆, Primary Measurement Standard

N-Phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]-2-furancarboxamide-¹³C₆ HCl

Dreduct No.		ISO 17034
Product No.:	F-064-1ML	ISO/IEC 17025
Lot No.:	FC01041902	130/120 17023
Description of CRM:	Furanyl fentanyl- $^{13}C_6$ HCl in Methanol (Solution)	ISO 13485
	Nominal concentration is adjusted for HCl content.	ISO 14001
Retest Date:	September 2021 See Section "Stability Assessment".	ISO 9001
Storage:	Store unopened in freezer (-10 °C to -25 °C).	1101
Shipping:	Ambient. See Section "Stability Assessment".	•HCI
Chemical formula:	$C_{18}^{13}C_{6}H_{26}N_{2}O_{2} \bullet HCI$	N [×]
CAS No.:	NA	
Regulatory:	USDEA Schedule I/9834	

Analyte	Certified Concentration \pm associated uncertainty U, $u=k*u$ (k=2)
Furanyl fentanyl- ¹³ C 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. Nominal concentration is adjusted for HCl 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 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.



September 28, 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

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 calcuated based on: the actual mass; Mass balance purity factor of the analyte(s); measured mass of the solution; and the density of the pure diluent at 20°C.
- Fill volume is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- Concentration is verified against an independently prepared calibration solution gravimetrically prepared.
- Additional certification information available upon request.

Solution Standard Verification

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

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

Standard Solution	Assay Parameters	Calibration Curve	
Analysis Method:	HPLC/UV	Calibration Curve:	Linear Regression
Column:	Ascentis Express Phenyl-Hexyl,	Number of Points:	4
Mobile Phase:	Acetonitrile:0.1% Phosphoric acid in Water (35:65)	Linearity (r):	1.000
Flow Rate:	1.5 mL/min		
Wavelength:	210 nm		
	Verified Concentratio	n (ma/ml) 9	&RSD - Homogeneity

		Vermed Concentration (mg/mL)	WKSD - Holliogeneity
Standard Solution	Lot Number	Actual Results	Actual Results
New Lot	FC01041902	1.001	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 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:	Furanyl fentanyl- ¹³ C ₆ HCl FC10101802 C ₁₈ ¹³ C ₆ H ₂₆ N ₂ O ₂ • HCl	Molecular Weig Molecular Weig Salt Adjustme	ght (base): ght (salt): nt:	380.43 416.89 1.096
CAS Number:	NA			
	Material Characte	erization Summary		
Analytical Test		Method	Res	sults
Primary Chromatographic	Purity by HPLC/UV Analysis	SP10-0102	99.	.3%
Secondary Chromatograp	hic Purity by GC/FID Analysis	SP10-0101	99.	.3%
Identity by LC/MS Analysi	S	SP10-0107	Consistent w	vith Structure
			0.00% 13	C ₀ vs ¹³ C ₆
		SP10-0107	0.00% ¹³ C ₀	0.04% ¹³ C ₄
Isotopic Purity and Distrib	oution by LC/MS SIM Analysis		0.00% ¹³ C ₁	2.03% ¹³ C ₅
			0.00% ¹³ C ₂	97.93% ¹³ C ₆
			0.00% ¹³ C ₃	
Identity by ¹ H-NMR Analy	sis	USP <761>, SP10-0116	Consistent w	vith Structure
Residual Solvent Analysis	by GC/FID Headspace	AM1087 ¹	0.7	7%
Residual Water Analysis by Karl Fischer Coulometry		AM1346 ¹	Below Quantitation Limit	
Inorganic Content by Micr	oash Analysis	SP10-0135	< 0	.2%
Mass Balance Purity Facto	r		98.4	49%

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:	Aso 2.7	centis Exp 7 um, 3.0	oress Pl x 100	henyl-He mm	xyl,
Mobile Phas	se: A:	Acetonit	rile		
	B:	0.1% Ph	osphor	ic acid in	Water
Gradient:	Tim	ne (min)	% A	% B	
		0.0	10	90	
		8.0	70	30	
		10.0	70	30	
		10.1	10	90	
Flow Rate:	0.7	′ mL/min			
Wavelength	1: 21	0 nm			
Sample Nar Acquired:	ne: FC De	10101802 cember 0	2 4, 2018	3	
Peak #	Ret Time	e A	rea %)	
1	3.89		0.14		
2	3.98		0.04		
3	4.50		99.25		
4	4.87		0.03		
5	4.99		0.04		
6	5.29		0.06		
7	5.43		0.41		
8	5.77		0.01		

0.01

GC/FID



Column: Temp Prog Injector Te Detector T	DB-5m 1.5 µm 60°C to hold 27 emp: Cool-or femp: 325°C	DB-5ms, 30 m x 0.53 mm ID, 1.5 µm film thickness 60°C to 300°C at 20°C/min hold 27 min Cool-on-Column 325°C	
Sample Na	me: FC1010)1802	
Acquired:	Novem	ber 30, 2018	
Peak #	Ret Time	Area %	
		0.05	
1	11.52	0.05	
1 2	11.52 11.97	0.16	
1 2 3	11.52 11.97 13.95	0.05 0.16 0.00	
1 2 3 4	11.52 11.97 13.95 15.75	0.05 0.16 0.00 99.27	
1 2 3 4 5	11.52 11.97 13.95 15.75 16.54	0.05 0.16 0.00 99.27 0.04	
1 2 3 4 5 6	11.52 11.97 13.95 15.75 16.54 16.83	0.05 0.16 0.00 99.27 0.04 0.01	
1 2 3 4 5 6 7	11.52 11.97 13.95 15.75 16.54 16.83 17.05	0.05 0.16 0.00 99.27 0.04 0.01 0.06	
1 2 3 4 5 6 7 8	11.52 11.97 13.95 15.75 16.54 16.83 17.05 17.51	0.05 0.16 0.00 99.27 0.04 0.01 0.06 0.40	

6.15

9

Residual Solvent Analysis by GC/FID Headspace



Instrument:

JEOL ECS 400

¹H NMR



LC/MS



Isotopic Purity by LC/MS SIM



Stability

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

Short Term Stability: A summary of accelerated stability findings for a related product (F-046-0.5ML, Furanyl fentanyl 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	
Room Temperature	21°C	after 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 20 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	January 22, 2019	Initial version.
01	January 30, 2020	Revised Retest Date from March 2020 to December 2020.
02	September 28, 2020	Revised Retest Date from December 2020 to September 2021.



Certified Reference Material - Certificate of Analysis

para-Fluorobutyryl fentanyl, Primary Measurement Standard

N-(4-Fluorophenyl)-N-(1-phenethylpiperidin-4-yl)butyramide

4-Fluorobutyryl fentanyl (4-FBl	, 4F-BF); para-Fluorobutyryl fentanyl (p-FBF); p-Fluorobutyry	l fentanyl (p-FBF)	ISO 17034
Product No.:	F-065-1ML		ISO/IEC 17025
Lot No.:	FC01071902		150 12495
Description of CRM:	para-Fluorobutyryl fentanyl in Methanol (Solution)		130 13465
Retest Date:	January 2022 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"		
Chemical formula:	C ₂₃ H ₂₉ FN ₂ O F		
CAS No.:	244195-31-1		
Regulatory:	USDEA Schedule I	\wedge	
	H	$_{13}C^{-} \sim 0$	

Analyte	Certified Concentration \pm associated uncertainty U, u=k*u (k=2)
para-Fluorobutyryl fentanyl	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 3.
Measurement method:	The certified value is calculated from high precision weighing of thoroughly characterized starting material. See "Details about certification process" on page 3.
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 02, 2021

Issue Date

Cerilliant Quality

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 calcuated based on: the actual mass; Mass balance purity factor of the analyte(s); measured mass of the solution; and the density of the pure diluent at 20°C.
- Fill volume is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- Concentration is verified against an independently prepared calibration solution gravimetrically prepared.
- Additional certification information available upon request.

Solution Standard Verification

Concentration accuracy and within- and between-bottle homogeneity 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
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 (35:65)	Linearity (r) :	1.000
Flow Rate:	1.5 mL/min		
Wavelength:	210 nm		
	Verified Concentration	(ma/ml) %	RSD - Homogeneity

		vermed Concentration (mg/mL)	%KSD - Homogeneity
Standard Solution	Lot Number	Actual Results	Actual Results
New Lot	FC01071902	0.989	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:	Material Name:para-Fluorobutyryl fentanylMaterial Lot:FC09241801		iula: C ₂₃ H ₂₉ FN ₂ O 244195-31-1 ght: 368.49		N ₂ O -31-1
	Material Characte	erization Summary			
Analytical Test		Method		Results	
Primary Chromatographi	c Purity by HPLC/UV Analysis	SP10-0102		99.7% ¹	
Secondary Chromatogra	phic Purity by GC/FID Analysis	SP10-0101		99.7%	
Identity by LC/MS Analy	sis	SP10-0107	Con	Consistent with Structure	
Identity by ¹ H-NMR Analysis		USP <761>, SP10-0116	Con	Consistent with Structure	
Residual Solvent Analysis by GC/FID Headspace		AM1087 ²		None Detected	
Residual Water Analysis by Karl Fischer Coulometry		AM1346 ²		Not Detect	ed
				Calculated	Analyzed
Elemental Analysis		Outcoursed	С	74.97%	75.25%
Elemental Analysis		Outsourced	н	7.93%	7.90%
			N	7.60%	7.82%
Mass Balance Purity Fact	tor			99.65%	

¹ 0.01% para-Fluorofentanyl and 0.06% Butyryl fentanyl 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:	Ascenti	s Express C	18, 2.7	um,
	3.0 x 10	00 mm		
Mobile Phas	se: A: Acet	onitrile		
	B: 0.1%	6 Phosphori	c acid in	Water
Gradient:	Time (n	nin) %A	% B	
	0.0	10	90	-
	8.0	70	30	
	10.0	70	30	
	10.1	10	90	
Flow Rate:	0.7 mL/	/min		
Wavelength	1: 210 nm	l		
Sample Nar	ne: FC0924	1801		
Acquired:	Eobruar	V 2E 2010		
Acquireat	i ebiuai	y 25, 2019		
Acquireur	i ebi udi	y 25, 2019		
Peak #	Ret Time	• 23, 2019 Area %	0	
Peak #	Ret Time 4.69	Area % 0.01	<u> </u>	
Peak # 1 2	Ret Time 4.69 4.92	Area % 0.01 0.02)	
Peak #	Ret Time 4.69 4.92 4.95	Area % 0.01 0.02 0.06		
Peak #	Ret Time 4.69 4.92 4.95 5.04	Area % 0.01 0.02 0.06 99.65	<u>.</u>	
Peak # 1 2 3 4 5	Ret Time 4.69 4.92 4.95 5.04 5.31	Area % 0.01 0.02 0.06 99.65 0.02	<u>)</u>	
Peak # 1 2 3 4 5 6	Ret Time 4.69 4.92 4.95 5.04 5.31 5.34	Area % 0.01 0.02 0.06 99.65 0.02 0.01		
Peak # 1 2 3 4 5 6 7	Ret Time 4.69 4.92 4.95 5.04 5.31 5.34 5.38	Area % 0.01 0.02 0.06 99.65 0.02 0.01 0.01		
Peak # 1 2 3 4 5 6 7 8	Ret Time 4.69 4.92 4.95 5.04 5.31 5.34 5.38 5.85	Area % 0.01 0.02 0.06 99.65 0.02 0.01 0.01 0.05		
Peak # 1 2 3 4 5 6 7 8 9	Ret Time 4.69 4.92 4.95 5.04 5.31 5.34 5.38 5.85 6.10	Area % 0.01 0.02 0.06 99.65 0.02 0.01 0.01 0.05 0.01		
Peak # 1 2 3 4 5 6 7 8 9 10	Ret Time 4.69 4.92 4.95 5.04 5.31 5.34 5.38 5.85 6.10 6.22	Area % 0.01 0.02 0.06 99.65 0.02 0.01 0.01 0.05 0.01 0.03		
Peak # 1 2 3 4 5 6 7 8 9 10 11	Ret Time 4.69 4.92 4.95 5.04 5.31 5.34 5.85 6.10 6.22 6.40	Area % 0.01 0.02 0.06 99.65 0.02 0.01 0.01 0.05 0.01 0.03 0.03		

Peak 1 is identified as para-Fluorofentanyl Peak 3 is identified as Butyryl fentanyl

GC/FID



Column:	DB-35m	is, 30 m x 0.53 mm	ID,	
	1.0 µm	film thickness		
Temp Prog	ram: 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	emp: Cool-on	-Column		
Detector To	emp: 325°C			
Sample Na	me: FC0924	1801		
Acquired:	Februar	y 27, 2019		
Peak #	Ret Time	Area %		
1	5.47	0.00		
2	10.37	0.01		
3	17.13	0.02		
4	18.74	0.07		
5	21.49	99.73		
6	21.80	0.05		

22.78

23.24

24.65

26.10

Residual Solvent Analysis by GC/FID Headspace



Column:		DB-ALC1 30 m x 0.5	53 mm,
Temp Program:		40°C hold 12 min to 40°C/min hold 5.5 r	220°C at nin
Carrier Gas:		Helium	
Flow Rat	e:	2.0 mL/min	
Detector	Heater Temp:	250°C	
Injector:		Headspace Sampler	
HS Oven	Temp:	60°C	
Vial Equi	libration:	10 minutes	
Sample N	Name:	FC09241801	
Acquired	:	February 26, 2019	
Peak	Compound	Area	Weight %
1	NMP	NA	NA
Total			ND
		ND - None Dete	cted

0.01

0.03

0.05

0.03

7

8

9

10



LC/MS

Column:	Kinetex C18,	2.6 µn	n, 2.1 x 50 mm	Flow Rate:	0.5 mL/min
Mobile Phase:	A: 0.1% Formic acid in Water		Scan Range:	100-1000 amu	
	B: Acetonitri	le		Ionization:	Electrospray, Positive Ion
Gradient:	Time (min)	% A	% B	Instrument:	Agilent 6410A
	0.0	80	20		Mass Spectrometer
	5.0	20	80	Acquired:	February 26, 2019
	6.0	20	80		
	7.0	80	20		
	11.0	80	20		



Stability

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

Short Term Stability: A summary of accelerated stability findings for 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 22 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 25, 2019	Initial version.
01	February 02, 2021	Updated Retest Date of February 2021 to January 2022.



Certified Reference Material - Certificate of Analysis

para-Fluorobutyryl fentanyl-¹³C₆, Primary Measurement Standard

	$N-(4-Fluorophenyl)-N-(1-phenethylpiperidin-4-yl)butyramide- {}^{13}C_{6}$	Cerilliant Quality
Product No.:	F-066-1ML	
Lot No.:	FC01031902	ISO 17034
Description of CRM	para-Fluorobutyryl fentanyl- $^{13}C_6$ in Methanol (Solution)	ISO/IEC 17025
Retest Date:	November 2021 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:	$C_{17}^{13}C_6H_{29}N_2OF$	
CAS No.:	NA H ₃ C N A	
Regulatory:	USDEA Schedule I	
	Ť	

Analyte		Certified Concentration \pm associated uncertainty U, $u=k*u$ (k=2)	
para-Fluorobutyryl fe	entanyl- ¹³ C ₆	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 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:	$1 \ \mu L$ for quantitat	ive applications	
Instructions for handling and correct use:	Concentration is of solvents and reside Users should quare laboratory practice 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 ses 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 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 nee material producer AR-1353 in accordance with ISO 17034 sting laboratory AT-1352 according to ISO/IEC 17025.	



Darron Ellsworth, Quality Assurance Manager

December 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.

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 (35:65)	Linearity (r) :	1.000
Flow Rate:	1.5 mL/min		
Wavelength:	210 nm		
	Verified Concentratior	. (mg/mL) %	RSD - Homogeneity

		Verified Concentration (ing/ine)	Tomogenery
Standard Solution	Lot Number	Actual Results	Actual Results
New Lot	FC01031902	0.998	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: Material Lot:	ne: para-Fluorobutyryl fentanyl- ¹³ C ₆ Chemical Fe FC10151802 CAS Number Molecular V		nula: ght:	C ₁₇ ¹³ C NA 374.44	5H29N2OF
	Material Characte	erization Summary			
Analytical Test		Method		Result	S
Primary Chromatographi	c Purity by HPLC/UV Analysis	SP10-0102		99.7%	1
Secondary Chromatograp	phic Purity by GC/FID Analysis	SP10-0101		99.7%	D
Identity by LC/MS Analys	sis	SP10-0107	Con	sistent with	Structure
			C	0.00% ¹³ C ₀	vs ¹³ C ₆
		SP10-0107	0.00%	% ¹³ C ₀	0.19% ¹³ C ₄
Isotopic Purity and Distri	bution by LC/MS SIM Analysis		0.00%	∕₀ ¹³ C ₁	4.05% ¹³ C ₅
			0.00%	⁄o ¹³ C ₂	99.76% ¹³ C ₆
			0.01%	6 ¹³ C ₃	
Identity by ¹ H-NMR Analy	ysis	USP <761>, SP10-0116	Con	sistent with	Structure
Residual Solvent Analysis	s by GC/FID Headspace	AM1087 ²	None Detected		ected
Residual Water Analysis	by Karl Fischer Coulometry	AM1346 ²	Belo	w Quantita	tion Limit
				Calculated	Analyzed
Elemental Analysis		Outcoursed	С	54.53%	74.08%
Elemental Analysis		Outsourcea	Н	7.81%	7.62%
			N	7.48%	7.67%
Mass Balance Purity Fact	:or			99.669	6

¹ 0.05% Butyryl fentanyl and no Fentanyl or para-Fluorofentanyl 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

- 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 C	18, 2.7	um,
Makila Dha	3.0 X 10			
Mobile Phas	se: A: Acet	onitrile		
	B: 0.1%	Phosphori	c acid in	Water
Gradient:	lime (m	11n) % A	% B	-
	0.0	10	90	
	8.0	70	30	
	10.0	70	30	
	10.1	10	90	
Flow Rate:	0.7 mL/	'min		
Wavelength	h: 210 nm			
Sample Na	me: FC1015	1802		
Acquirod	Lepan	February 26, 2019		
Acquireu.	Februar	y 26, 2019		
Acquireu.	rebruar	y 26, 2019		
Peak #	Ret Time	Area %		
Peak #	Ret Time 4.73	y 26, 2019 Area % 0.01)	
Peak #	Ret Time 4.73 4.85	y 26, 2019 Area % 0.01 0.01		
Peak #	Ret Time 4.73 4.85 4.95	Area % 0.01 0.01 0.04	<u>, </u>	
Peak # 1 2 3 4	Ret Time 4.73 4.85 4.95 4.98	Area % 0.01 0.01 0.04 0.05	,	
Peak # 1 2 3 4 5	Ret Time 4.73 4.85 4.95 4.95 5.07	Area % 0.01 0.01 0.04 0.05 99.62		
Peak # 1 2 3 4 5 6	Ret Time 4.73 4.85 4.95 4.98 5.07 5.39	Area % 0.01 0.01 0.04 0.05 99.62 0.02		
Peak # 1 2 3 4 5 6 7	Ret Time 4.73 4.85 4.95 4.95 5.07 5.39 5.47	Area % 0.01 0.01 0.04 0.05 99.62 0.02 0.01	,	
Peak # 1 2 3 4 5 6 7 8	Ret Time 4.73 4.85 4.95 4.98 5.07 5.39 5.47 5.53	Area % 0.01 0.04 0.05 99.62 0.02 0.01 0.01	,	
Peak # 1 2 3 4 5 6 7 8 9	Ret Time 4.73 4.85 4.95 4.98 5.07 5.39 5.47 5.53 5.84	Area % 0.01 0.01 0.04 0.05 99.62 0.02 0.01 0.01 0.05		
Peak # 1 2 3 4 5 6 7 8 9 10	Ret Time 4.73 4.85 4.95 4.98 5.07 5.39 5.47 5.53 5.84 5.90	Area % 0.01 0.01 0.04 0.05 99.62 0.02 0.01 0.01 0.05 0.03		
Peak # 1 2 3 4 5 6 7 8 9 10 11	Ret Time 4.73 4.85 4.95 4.98 5.07 5.39 5.47 5.53 5.84 5.90 6.06	Area % 0.01 0.01 0.04 0.05 99.62 0.02 0.01 0.01 0.05 0.03 0.15	,	

Peak 4 is identified as Butyryl fentanyl

GC/FID



Residual Solvent Analysis by GC/FID Headspace

FID1 A, (F-002-48-RMF-070 FC10151802 10 37mg.D)	Column:		DB-ALC1 30 m x 0	.53 mm,
Norm. 1 500 -			3 µm film thicknes	S
	Temp Pr	ogram:	40°C noid 12 min t	to 220°C at
	Carrier (2261	40°C/Min noia 5.5	min
400 -	Flow Rat	jas. te:	2.0 ml/min	
	Detector	Heater Temp:	250°C	
-	Injector	:	Headspace Sample	r
300 -	HS Oven	Temp:	60°C	
	Vial Equ	ilibration:	10 minutes	
200-			5010151000	
	Sample	Name:	FC10151802	
	Acquired	1:	February 27, 2019	
100 -	Peak	Compound	Area	Weight %
	1	NMP	NA	NA
0-	Total			ND
0 2.5 5 7.5 10 12.5 15 17.5 20 min			ND - None Det	ected

14

28.01

0.01



LC/MS



Isotopic Purity by LC/MS SIM

µm, 2.1 x 50 mm	Flow Rate:	0.5 mL/min
icid in Water	Scan Range:	369-375 amu
	Ionization:	Electrospray, Negative Ion
А %В	Instrument:	Agilent 6410A
20		Mass Spectrometer
80	Acquired:	February 26, 2019
80		
20		
20		
	μm, 2.1 x 50 mm cid in Water <u>A % B</u> 20 80 80 20 20 20	μm, 2.1 x 50 mmFlow Rate: Scan Range: Ionization: Instrument:A% BInstrument:2080Acquired:802020202020



Stability

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

Short Term Stability: A summary of accelerated stability findings for a related product (F-048-0.5ML, para-Fluorobutyryl fentanyl) is listed below.

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 20 months has been established for this product 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 15, 2019	Initial version.
01	April 17 2020	Added Long Term Stability data.
01	April 17, 2020	Updated Retest Date of May 2020 to February 2021.
02	December 09, 2020	Updated Retest Date of February 2021 to November 2021.



Certified Reference Material - Certificate of Analysis

para-Fluorofentanyl, Primary Measurement Standard

N-(4-Fluorophenyl)-N-[1-(2-phenylethyl)-4-piperidinyl]-propanamide; p-Fluoro fentanyl (p-FF); **Cerilliant Quality**

4-Fluoro fentanyl (4-FF)	
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				ISO 17034
Product No.:	F-067-1ML			ISO/IEC 17025
Lot No.:	FC12261801			
Description of CRM:	para-Fluorofe	ntanyl in Methanol (Solution)		ISO 13485
Retest Date:	July 2022	See Section "Stability Assessr	nent".	ISO 14001
Storage:	Store unopen	ed in freezer (-10 °C to -25 °C).		ISO 9001
Shipping:	Ambient.	See Section "Stability Assessment".	0 ($\sim_N \sim$
Chemical formula:	$C_{22}H_{27}FN_2O$		H₃C↓↓N↓	
CAS No.:	90736-23-5		, i i i i i i i i i i i i i i i i i i i	
Regulatory:	USDEA Sched	lule I/9812		÷
			F	

Analyte		Certified Concentration \pm associated uncertainty U, $u=k*u$ (k=2)
para-Fluorofer	itanyl	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	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 quantitative applications	
Instructions for handling and correct use:	Concentration is corrected for chromatographic purity, residual solvents and residual inorganics. No adjustment required before use. Users should quantitatively transfer desired volume using established good laboratory practices to spike into matrix or to dilute to the desired concentration. Each ampoule is intended for one-time use.	
Health and safety information:	Danger. Please refer to the Safety Data Sheet for detailed information about the nature of any hazard and appropriate precautions to be taken.	
Accreditation:	Cerilliant Corp. is registered referent and registered test	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.



Darron Ellsworth, Quality Assurance Manager

February 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 calcuated based on: the actual mass; Mass balance purity factor of the analyte(s); measured mass of the solution; and the density of the pure diluent at 20°C.
- Fill volume is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- Concentration is verified against an independently prepared calibration solution gravimetrically prepared.
- Additional certification information available upon request.

Solution Standard Verification

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

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 (35:65)	Linearity (r) :	1.000
Flow Rate:	1.5 mL/min		
Wavelength:	210 nm		
	Verified Concentration	(ma/ml) %	RSD - Homogeneity

		verified Concentration (mg/mL)	%KSD - Homogeneity
Standard Solution	Lot Number	Actual Results	Actual Results
New Lot	FC12261801	1.009	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: Material Lot:	para-Fluorofentanyl FC10011802	Chemical Form CAS Number: Molecular Weig	ıula: ght:	C ₂₂ H ₂₇ Ff 90736-2 354.46	N ₂ O 23-5	
Material Characterization Summary						
Analytical Test		Method		Results		
Primary Chromatographic Purity by HPLC/UV Analysis		SP10-0102	99.6% ¹			
Secondary Chromatographic Purity by GC/FID Analysis		SP10-0101	99.8% ²			
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 ³	None Detected			
Residual Water Analysis by Karl Fischer Coulometry		AM1346 ³	Below Quantitation Limit			
				Calculated	Analyzed	
		Outrouwood	С	74.55%	74.38%	
Elemental Analysis		Outsourced	н	7.68%	7.58%	
			N	7.90%	8.00%	
Mass Balance Purity Factor			99.64%			

¹ No Fentanyl detected by HPLC/UV analysis.

- ² 0.02% Fentanyl 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



Column:	Ascentis E	xpress C	oress C18, 2.7 µm,		
	3.0 x 100	3.0 x 100 mm			
Mobile Pha	se: A: Acetoni	A: Acetonitrile			
	B: 0.1% P	hosphori	c acid in	Water	
Gradient:	Time (min)) % A	% B		
	0.0	10	90	-	
	8.0	70	30		
	10.0	70	30		
	10.1	10	90		
Flow Rate:	0.7 mL/mi	0.7 mL/min			
Wavelengt	h: 210 nm				
Sample Na	me: FC100118	FC10011802			
Acquired:	December	05, 2018	3		
Peak #	Ret Time	Area %			
1	3.47	0.01			
2	3.69	0.01			
3	3.86	99.61			
4	4.15	0.32			
5	4.40	0.02			
6	4.70	0.01			
7	4.97	0.02			

4.97

GC/FID



Column: Temp Progr Injector Ter Detector Te Sample Nar Acquired:	DB-35r 1.0 µm 40°C to 200°C hold 16 mp: Cool-or mp: 325°C me: FC1001 Decem	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 300°C at 5°C/min hold 16 min Cool-on-Column 325°C FC10011802 December 04, 2018	
Peak #	Ret Time	Area %	
1	16.53	0.05	
2	19.65	0.01	
3	20.18	99.78	
4	20.60	0.01	
5	20.74	0.02	
6	24.28	0.14	

Peak #5 has been identified as Fentanyl

Residual Solvent Analysis by GC/FID Headspace



¹H NMR


LC/MS

Column:	Ascentis Express C18, 2.7 μm,			Flow Rate:	0.4 mL/min 100-1200 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:	December 05, 2018
	0.0	90	10				
	0.5	90	10				
	4.0	50	50				
	5.8	50	5U 10				
	8.0	90 90	10				
RMF-055 FC10011802			para	-Fluorofenta	anyl	C	cone Voltage: 15.00000000
W12051824 751 (2.817) Cn	n (748:756)						1: TOF MS ES+
100	355.2171	Theo Foun	retical [M d [M + H	1 + H]+: 3]+: 355.2	55.2186 171		1.06e6
8							
	356.2210	N					
	35/.226						•••••• m/z
100 200	300 400	50	0 60)0 70	008 0	900 100	0 1100

Stability

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

Short Term Stability: A summary of accelerated stability findings for 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 30 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	January 21, 2019	Initial version.
01	June 03, 2019	Corrected the spelling of the analyte name throughout the certificate.
02	February 06, 2020	Updated Retest Date of March 2020 to July 2022.



Certified Reference Material - Certificate of Analysis

para-Fluorofentanyl-¹³C₆, Primary Measurement Standard

N-(4-Fluorophenyl)-N-[1-(2-phenylethyl)-4-piperidinyl]propenamide- ${}^{13}C_6$

Product No.:	F-068-1ML	Cerilliant Quality
Lot No.:	FC01141904	
Description of CRM:	para-Fluorofentanyl- $^{13}C_6$ in Methanol (Solution)	ISO 17034
Retest Date:	November 2021 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:	$C_{16}^{13}C_{6}H_{27}N_{2}OF$	ISO 9001
CAS No.:	NA	
Regulatory:	USDEA Schedule I	

Analyte		Certified Concentration \pm associated uncertainty U, $u=k*u$ (k=2)	
para-Fluorofenta	nyl- ¹³ C ₆	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 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	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. 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 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.	



Darron Ellsworth, Quality Assurance Manager

December 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 calcuated based on: the actual mass; Mass balance purity factor of the analyte(s); measured mass of the solution; and the density of the pure diluent at 20°C.
- Fill volume is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- Concentration is verified against an independently prepared calibration solution gravimetrically prepared.
- Additional certification information available upon request.

Solution Standard Verification

Concentration accuracy and within- and between-bottle homogeneity 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
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 (35:65)	Linearity (r) :	1.000
Flow Rate:	1.2 mL/min		
Wavelength:	210 nm		
	Verified Concentration	(mg/mL) %	RSD - Homogeneity

		Vermed concentration (mg/me)	/oksb = noniogeneity
Standard Solution	Lot Number	Actual Results	Actual Results
New Lot	FC01141904	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:	para-Fluorofentanyl- ¹³ (FC10151801	C ₆ Chemical Fo CAS Numbe Molecular V	ormula: C ₁₆ ¹ er: NA Weight: 360	¹³ C ₆ H ₂₇ N ₂ OF .42
	Material Cha	racterization Summary		
Analytical Test		Method	Resu	lts
Primary Chromatograph Analysis	ic Purity by HPLC/UV	SP10-0102	98.4	%
Secondary Chromatogra Analysis	phic Purity by GC/FID	SP10-0101	98.7	%
Identity by LC/MS Analysis		SP10-0107	Consistent with Structure	
			0.00% ¹³ C	₀ vs ¹³ C ₆
Isotopic Purity and Distribution by LC/MS SIM			0.00% $^{13}\text{C}_{0}$ to $^{13}\text{C}_{1}$	2.80% ¹³ C ₅
Analysis		SP10-0107	0.03% $^{13}\text{C}_2$ to $^{13}\text{C}_3$	97.05% ¹³ C ₆
			0.09% ¹³ C ₄	
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 Coulomet		AM1346 ¹	Not Detected	
Mass Balance Purity Factor			98.45	5%

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:	Ascent	tis Express P	henyl-Hex	xyl,		
Mobile Pha	2./µn se: A:Ac	2.7 µm, 3.0 x 100 mm				
Hobile I ha	B: 0.1	B: 0.1% Phosphoric acid in Water				
Gradient:	Time (min) % A	% B			
	0.0) 10	90			
	8.0) 70	30			
	10.	0 70	30			
	10.	1 10	90			
Flow Rate:	0.7 ml	L/min				
Wavelengt	h: 210 nr	m				
Sample Na	me: FC101	51801				
Acquired:	Februa	ary 11, 2019				
"	- · -·	• • • •				
Peak #	Ret Time	Area %	_			
Peak #	Ret Time 3.41	Area %	_			
Peak #	Ret Time 3.41 4.22 4.74	Area %	-			
Peak #	Ret Time 3.41 4.22 4.74 5.00	Area % 0.01 0.01 0.03 08.40	-			
Peak # 1 2 3 4 5	Ret Time 3.41 4.22 4.74 5.00 5.35	Area % 0.01 0.03 98.49 0.09	-			
Peak # 1 2 3 4 5 6	Ret Time 3.41 4.22 4.74 5.00 5.35 5.44	Area % 0.01 0.03 98.49 0.09 0.68	-			
Peak # 1 2 3 4 5 6 7	Ret Time 3.41 4.22 4.74 5.00 5.35 5.44 5.55	Area % 0.01 0.03 98.49 0.09 0.68 0.01	-			
Peak # 1 2 3 4 5 6 7 8	Ret Time 3.41 4.22 4.74 5.00 5.35 5.44 5.55 5.63	Area % 0.01 0.01 0.03 98.49 0.09 0.68 0.01 0.01	-			
Peak # 1 2 3 4 5 6 7 8 9	Ret Time 3.41 4.22 4.74 5.00 5.35 5.44 5.55 5.63 5.91	Area % 0.01 0.01 0.03 98.49 0.09 0.68 0.01 0.01 0.01 0.03	-			
Peak # 1 2 3 4 5 6 7 8 9 10	Ret Time 3.41 4.22 4.74 5.00 5.35 5.44 5.55 5.63 5.91 5.99	Area % 0.01 0.03 98.49 0.09 0.68 0.01 0.01 0.03 0.11	_			
Peak # 1 2 3 4 5 6 7 8 9 10 11	Ret Time 3.41 4.22 4.74 5.00 5.35 5.44 5.55 5.63 5.91 5.99 6.12	Area % 0.01 0.01 0.03 98.49 0.09 0.68 0.01 0.01 0.01 0.03 0.11 0.47	_			
Peak # 1 2 3 4 5 6 7 8 9 10 11 12	Ret Time 3.41 4.22 4.74 5.00 5.35 5.44 5.55 5.63 5.91 5.99 6.12 6.20	Area % 0.01 0.03 98.49 0.09 0.68 0.01 0.01 0.03 0.11 0.47 0.01	_			

GC/FID



Column:	DB 1.5	3-5ms, 30 m x 0.53 mm ID, 5 um film thickness
Temp Prog	pram: 40 20 ho	°C to 200°C at 40°C/min 0°C to 300°C at 5°C/min Id 16 min
Detector T	emp: 32	5°C
Sample Na Acquired:	i me: FC Fel	10151801 bruary 12, 2019
Peak #	Ret Time	e Area %
1	7.95	0.00
2	8.78	0.00
3	8.91	0.00
4	15.77	0.03
5	15.8/	0.01
6	15.99	0.01
/	10.66	0.01
8	10.24	0.02
9	10.24	0.00
11	19.05	0.01
12	19.25	0.01
13	20.10	0.00
14	20.29	0.01
15	20.39	0.00
16	20.70	0.02
17	21.10	0.12
18	21.24	0.08
19	21.49	0.34
20	21.70	0.00
21	22.16	0.02
22	22.59	0.00
23	22.98	0.58
24	23.25	0.01
25	24.04	0.01
26	25.26	0.02
27	25.45	0.01



Residual Solvent Analysis by GC/FID Headspace





LC/MS



Isotopic Purity by LC/MS



Stability

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

Short Term Stability: A summary of accelerated stability findings for a related product (F-049-0.5ML, para-Fluorofentanyl) 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 20 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 13, 2019	Initial version.
01	Amril 17, 2020	Updated Retest Date of May 2020 to February 2021.
01 April 17, 2020		Added Long Term Stability data.
02	December 10, 2020	Updated Retest Date of February 2021 to November 2021.



Certified Reference Material - Certificate of Analysis

Fe	entanyl- ¹³ C ₆ , Primary Measurement Standard	Cerilliant Quality
	N-Phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]propenamide- ${}^{13}C_6$	ISO 17034
Product No.:	F-069-1ML	ISO/IEC 17025
Lot No.:	FC01071903	ISO 13485
Description of CRM:	Fentanyl- $^{13}C_6$ in Methanol (Solution)	10.0.1.0001
Retest Date:	October 2021 See Section "Stability Assessment".	ISO 14001
Storage:	Store unopened in freezer (-10 °C to -25 °C).	ISO 9001
Shipping:	Ship Ambient. See Section "Stability Assessment".	$\sim_N \sim$
Chemical formula:	$C_{16}^{13}C_{6}H_{28}N_{2}O$ $H_{3}C_{16}$	
CAS No.:	NA J*	Ĩ []
Regulatory:	USDEA Schedule II/9801	

Analyte		Certified Concentration \pm associated uncertainty U, $u=k*u$ (k=2)	
Fentanyl- ¹³	С ₆	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 μ L for quantitat	ive applications	
Instructions for handling and correct use:	Concentration is of solvents and reside Users should quar laboratory practice concentration. Ear 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 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 ice material producer AR-1353 in accordance with ISO 17034 sting laboratory AT-1352 according to ISO/IEC 17025.	



Darron Ellsworth, Quality Assurance Manager

October 27, 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 calcuated based on: the actual mass; Mass balance purity factor of the analyte(s); measured mass of the solution; and the density of the pure diluent at 20°C.
- Fill volume is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- Concentration is verified against an independently prepared calibration solution gravimetrically prepared.
- Additional certification information available upon request.

Solution Standard Verification

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

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 Cu	ırve
Analysis Method:	HPLC/UV	Calibration Cu	Irve: Linear Regression
Column:	Ascentis Express C18, 2.7 µm, 3.0 x 100 mm	Number of Poi	ints: 4
Mobile Phase:	Acetonitrile:0.1% Phosphoric acid in Water (30:70)	Linearity (r) :	1.000
Flow Rate:	1.5 mL/min		
Wavelength:	210 nm		
	Verified Concentratior	(mg/mL)	%RSD - Homogeneity

		Verified Concentration (ing/ine)	Juikob Holliogenery
Standard Solution	Lot Number	Actual Results	Actual Results
New Lot	FC01071903	0.994	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:Fentanyl-13C6Material Lot:FC10091801	aterial Name:Fentanyl-13C6Chemical Formulaaterial Lot:FC10091801CAS Number: Molecular Weight		^{.3} C ₆ H ₂₈ N ₂ O .43
Material Charac	terization Summary		
Analytical Test	Method	Results	
Primary Chromatographic Purity by HPLC/UV Analysis	SP10-0102	99.2% ¹	
Secondary Chromatographic Purity by GC/FID Analysis	SP10-0101	98.8% ²	
Identity by LC/MS Analysis	SP10-0107	Consistent with Structure	
		0.00% 13	C ₀ vs ¹³ C ₆
		0.00% ¹³ C ₀	0.05% ¹³ C ₄
Isotopic Purity and Distribution by LC/MS SIM Analysis	SP10-0107	0.00% ¹³ C ₁	3.09% ¹³ C ₅
		0.00% ¹³ C ₂	96.86% ¹³ C ₆
		0.00% ¹³ C ₃	
Identity by ¹ H-NMR Analysis	USP <761>, SP10-0116	Consistent w	ith Structure
Residual Solvent Analysis by GC/FID Headspace	AM1087 ³	0.12%	
Residual Water Analysis by Karl Fischer Coulometry	AM1346 ³	Not De	etected
Inorganic Content by Microash Analysis	SP10-0135	< 0.2%	
Mass Balance Purity Factor		99.()8%

¹ No 4-ANPP-¹³C₆ detected by HPLC/UV analysis.

² 0.01% 4-ANPP-¹³C₆ 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



Column:	Ascentis	Express C1	8, 2.7	μm,
	3.0 x 10	0 mm		
Mobile Pha	se: A: Aceto	onitrile		
	B: 0.1%	Phosphoric	acid in	Water
Gradient:	Time (m	in) %A	% B	
	0.0	10	90	-
	8.0	70	30	
	10.0	70	30	
	10.1	10	90	
Flow Rate:	0.7 mL/	min		
Wavelengtl	h: 210 nm			
Sample Na	me: FC1009:	1801		
Acquired:	Decemb	er 19, 2018		
Peak #	Ret Time	Area %		
Peak #	Ret Time 2.27	Area %		
Peak # 1 2	Ret Time 2.27 3.06	Area % 0.01 0.28		
Peak # 1 2 3	Ret Time 2.27 3.06 3.71	Area % 0.01 0.28 99.20		
Peak # 1 2 3 4	Ret Time 2.27 3.06 3.71 4.01	Area % 0.01 0.28 99.20 0.05		
Peak # 1 2 3 4 5	Ret Time 2.27 3.06 3.71 4.01 4.07	Area % 0.01 0.28 99.20 0.05 0.01		
Peak # 1 2 3 4 5 6	Ret Time 2.27 3.06 3.71 4.01 4.07 4.13	Area % 0.01 0.28 99.20 0.05 0.01 0.02		
Peak # 1 2 3 4 5 6 7	Ret Time 2.27 3.06 3.71 4.01 4.07 4.13 4.28	Area % 0.01 0.28 99.20 0.05 0.01 0.02 0.01		
Peak # 1 2 3 4 5 6 7 8	Ret Time 2.27 3.06 3.71 4.01 4.07 4.13 4.28 4.31	Area % 0.01 0.28 99.20 0.05 0.01 0.02 0.01 0.02 0.01 0.02		
Peak # 1 2 3 4 5 6 7 8 9	Ret Time 2.27 3.06 3.71 4.01 4.07 4.13 4.28 4.31 4.39	Area % 0.01 0.28 99.20 0.05 0.01 0.02 0.01 0.02 0.01 0.02 0.01		
Peak # 1 2 3 4 5 6 7 8 9 10	Ret Time 2.27 3.06 3.71 4.01 4.07 4.13 4.28 4.31 4.39 4.45	Area % 0.01 0.28 99.20 0.05 0.01 0.02 0.01 0.02 0.01 0.02 0.01 0.02 0.01 0.01		
Peak # 1 2 3 4 5 6 7 8 9 10 11	Ret Time 2.27 3.06 3.71 4.01 4.07 4.13 4.28 4.31 4.39 4.45 4.57	Area % 0.01 0.28 99.20 0.05 0.01 0.02 0.01 0.02 0.01 0.02 0.01 0.01		
Peak # 1 2 3 4 5 6 7 8 9 10 11 12	Ret Time 2.27 3.06 3.71 4.01 4.07 4.13 4.28 4.31 4.39 4.45 4.57 4.74	Area % 0.01 0.28 99.20 0.05 0.01 0.02 0.01 0.02 0.01 0.02 0.01 0.01		

5.14

6.79

14

15

0.01

0.11

GC/FID



Column:	DB-5ms, 30 m x 0.53 mm ID,
Temp Program:	1.5 μm film thickness 40°C to 200°C at 40°C/min 200°C to 300°C at 5°C/min
Injector Temp: Detector Temp:	hold 16 min Cool-on-Column 325°C
Sample Name: Acquired:	FC10091801 December 17, 2018

Peak #	Ret Time	Area %
1	4.87	0.00
2	4.96	0.00
3	5.09	0.01
4	5.44	0.02
5	7.64	0.01
6	8.20	0.02
7	8.25	0.02
8	8.67	0.63
9	9.36	0.00
10	10.59	0.03
11	12.54	0.06
12	13.37	0.02
13	13.78	0.00
14	14.32	0.01
15	14.88	0.00
16	15.08	0.01
17	15.26	0.01
18	15.64	0.01
19	15.82	0.00
20	15.93	0.00
21	17.85	0.00
22	18.19	0.00
23	18.97	98.85
24	19.74	0.01
25	20.16	0.02
26	20.66	0.09
27	21.17	0.14
28	21.65	0.00
29	22.40	0.02
30	23.15	0.01
31	24.80	0.01

Peak #17 has been identified as 4-ANPP-¹³C₆

Residual Solvent Analysis by GC/FID Headspace



Instrument:

JEOL ECS 400

¹H NMR



LC/MS



Isotopic Purity by LC/MS SIM



Stability

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

Short Term Stability: A summary of accelerated stability findings for a related product (F-013, Fentanyl) 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)			

Long Term Stability: Long term stability has been assessed for Freezer storage (-10 °C to -25 °C) conditions. Stability of a minimum of 20 months has been established for a related product (F-013, Fentanyl) 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 05, 2019	Initial version.
01	March 24, 2020	Updated Retest Date of April 2020 to January 2021.
02	October 27, 2020	Updated Retest Date of January 2021 to October 2021.



Certified Reference Material - Certificate of Analysis

(±)-beta-Hydroxythiofentanyl, Primary Measurement Standard

 (\pm) -*N*-[1-[2-Hydroxy-2-(2-thienyl)ethyl]-4-piperidinyl]-*N*-phenyl-propanamide HCl; beta-Hydroxythio fentanyl; b-Hydroxythio fentanyl; (\pm) -b-Hydroxythiofentanyl HCl; (\pm) - β -Hydroxythiofentanyl HCl

Product No.:	H-137-1ML	Cerilliant Quality
Lot No.:	FC12261806	ISO 17034
Description of CRM:	(±)-beta-Hydroxythiofentanyl HCl in Methanol (Solution)	ISO /IEC 17025
	Nominal concentration is adjusted for HCl content	ISO/IEC 17025
	Nominal concentration is adjusted for their content.	ISO 13485
Retest Date:	November 2021 See Section "Stability Assessment".	100 1 4001
Storage:	Store unopened in freezer (-10 °C to -25 °C).	150 14001
Shipping:	Ship cold. See Section "Stability Assessment".	ISO 9001
Chemical formula:	$C_{20}H_{26}N_2O_2S \bullet HCI$	
CAS No.:	NA $H_{3}C_{2}$ $H_{3}C_{4}$ $H_{3}C_{5}$ H_{3} H_{3	
Regulatory:	USDEA Schedule I	

Analyte		Certified Concentration \pm associated uncertainty U, $u=k*u$ (k=2)	
(±)-beta-Hydroxyth	iofentanyl	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 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		
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 referent and registered test	accredited by the US accreditation authority ANAB as a net are as a net as a net are as a net an net are as a net as a net are as a net are as a net are as a net	



Darron Ellsworth, Quality Assurance Manager

December 15, 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 calcuated based on: the actual mass; Mass balance purity factor of the analyte(s); measured mass of the solution; and the density of the pure diluent at 20°C.
- Fill volume is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- Concentration is verified against an independently prepared calibration solution gravimetrically prepared.
- Additional certification information available upon request.

Solution Standard Verification

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

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	L8, 2.7 μm, 3.0 x 100 mm	Number of	Points:	4
Mobile Phase:	Acetonitrile:0.1% P (30:70)	hosphoric acid in Water	Linearity (r):	1.000
Flow Rate:	1.5 mL/min				
Wavelength:	210 nm				
		Verified Concentration	(mg/mL)	%F	RSD - Homogeneity

Standard Solution	Lot Number	Actual Results	Actual Results
New Lot	FC12261806	1.003	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 and salt adjustment are utilized to calculate the weighing adjustment necessary to ensure accuracy of the solution standard concentration.

Material Name:	(±)-beta-Hydroxythiofentar	iyi HCi Molecular Weig	ght (ba:	se): 358	.50
Material Lot:	FC10291802	Molecular Wei	Molecular Weight (salt):		.96
Chemical Formula:	$C_{20}H_{26}N_2O_2S \bullet HCI$	Salt Adjustmer	nt:	1.10)2
CAS Number:	NA				
	Material Characterization Summary				
Analytical Test		Method		Results	
Primary Chromatographic	Purity by HPLC/UV Analysis	SP10-0102		99.5% ¹	
Secondary Chromatograph	nic Purity by GC/FID Analysis	SP10-0101		98.2%	
Identity by LC/MS Analysi	s	SP10-0107 Co		Consistent with Structure	
Identity by ¹ H-NMR Analysis		USP <761>, SP10-0116 Consistent with Stru		Structure	
Residual Solvent Analysis by GC/FID Headspace		AM1087 ²		None Detec	ted
Residual Water Analysis b	y Karl Fischer Coulometry	AM1346 ²	Belo	ow Quantitati	on Limit
Inorganic Content by Micr	oash Analysis	SP10-0135	< 0.2%		
				Calculated	Analyzed
Flomontal Analysis		Outcoursed	С	60.82%	60.77%
Elemental Analysis		Outsourceu	н	6.89%	6.84%
			N	7.09%	7.22%
Mass Balance Purity Factor				99.51%	

¹ 0.05% Norfentanyl 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:	Asce 2.7 L	ntis Exp Im. 3.0	oress Pł x 100 i	nenyl-He mm	xyl,
Mobile Phas	se: A: A	cetonitr	ile		
	В: 0.	1% Pho	osphorio	c acid in	Water
Gradient:	Time	(min)	% A	% B	
	0	.0	10	90	-
	8	.0	70	30	
	10	0.0	70	30	
	10).1	10	90	
Flow Rate:	0.7 n	nL/min			
Wavelength	: 210	าฑ			
Samnle Nan	EC10	201901	2		
Sample Nan		291002	2010		
Acquireu.	Janua	ary 14,	2019		
Peak #	Ret Time	A	rea %		
1	2.79		0.05		
2	3.53		0.01		
3	4.04		99.63		
4	4.33		0.23		
5	4.40		0.02		
6	4.46		0.02		
7	5.03		0.02		
8	7.10		0.02		
9	7.80		0.01		

Peak #1 has been identified as Norfentanyl



	Column:	DB-35 1.0 μn	ms, 30 m x 0.53 mm ID, n film thickness		
	Temp Prog	ram: 60°C t hold 2	o 300°C at 20°C/min 7 min		
	Injector Te	emp: Cool-o	Cool-on-Column		
	Detector T	emp: 325°C			
	Sample Na	me: FC102	91802		
	Acquired:	Januar	ry 17, 2019		
	Peak #	Ret Time	Area %		
	1	10.23	0.01		
	2	12.50	0.03		
	3	12.56	0.05		
	4	17.12	98.16		
-	5	17.68	0.93		
	6	18.13	0.82		

Residual Solvent Analysis by GC/FID Headspace







Stability

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

Short Term Stability: A summary of accelerated stability findings for 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:	Ship cold.	

Long Term Stability: Long term stability has been assessed for Freezer storage (-10 °C to -25 °C) conditions. Stability of a minimum of 21 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
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Revision No.	Date	Reason for Revision
00	February 22, 2019	Initial version.
01	March 18, 2020	Revised Retest Date from April 2020 to February 2021.
01		Added Long Term Stability section.
02	December 15, 2020	Revised Retest Date from February 2021 to November 2021.



Certified Reference Material - Certificate of Analysis

(±)-beta-Hydroxythiofentanyl- ${}^{13}C_6$, Primary Measurement Standard

 (\pm) -N-[1-[2-Hydroxy-2-(2-thienyl)ethyl]-4-piperidinyl]-N-phenyl-propanamide-¹³C₆ HCl

Product No.:	H-138-1ML	Cerilliant Quality
Lot No.:	FC12261809	150 17034
Description of CRM:	(±)-beta-Hydroxythiofentanyl- ¹³ C ₆ HCl in Methanol (Solution)	130 17034
-	Nominal concentration is adjusted for HCl content	ISO/IEC 17025
	Nominal concentration is aujusted for her content.	ISO 13485
Retest Date:	November 2021 See Section "Stability Assessment".	100 10100
Storage:	Store unopened in freezer (-10 °C to -25 °C).	ISO 14001
Shipping:	Ambient See Section "Stability Assessment".	ISO 9001
Chemical formula:	$C_{14}^{13}C_{6}H_{26}N_{2}O_{2}S \bullet HCl$	
CAS No.:	NA H ₃ C h	
Regulatory:	USDEA Schedule I ***** • HCI	

Analyte		Certified Concentration ± associated uncertainty U, u=k*u (k=2)	
(±)-beta-Hydroxythio	fentanyl- ¹³ C ₆	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 a standards from NIST through an for a standard standard for a standard s	
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 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. 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.	



Det

December 04, 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 calcuated based on: the actual mass; Mass balance purity factor of the analyte(s); measured mass of the solution; and the density of the pure diluent at 20°C.
- Fill volume is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- Concentration is verified against an independently prepared calibration solution gravimetrically prepared.
- Additional certification information available upon request.
Solution Standard Verification

Concentration accuracy and within- and between-bottle homogeneity 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
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 (30:70)	Linearity (r) :	1.000
Flow Rate:	1.0 mL/min		
Wavelength:	210 nm		
	Verified Concentration	i (mg/mL) %	RSD - Homogeneity

			70KSD - Holliogeneity
Standard Solution	Lot Number	Actual Results	Actual Results
New Lot	FC12261809	1.008	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 and salt adjustment are utilized to calculate the weighing adjustment necessary to ensure accuracy of the solution standard concentration.

Material Name:	(±)-beta-Hydroxythiofentanyl- ¹³ C ₆ HCl	Molecular Weight (base):	364.45
Material Lot:	FC10291801	Molecular Weight (salt):	400.91
Chemical Formula:	$C_{14}^{13}C_{6}H_{26}N_{2}O_{2}S \bullet HCI$	Salt Adjustment:	1.100
CAS Number:	NA		

Material Characterization Summary					
Analytical Test	Method		Resu	ts	
Primary Chromatographic Purity by HPLC/UV Analysis	SP10-0102		98.7%	, ¹	
Secondary Chromatographic Purity by GC/FID Analysis	SP10-0101		98.90	%	
Identity by LC/MS Analysis	SP10-0107	Con	sistent wit	h Struc	ture
		C).01% ¹³ C ₀	vs ¹³ C ₆	5
		0.01%	∕₀ ¹³ C ₀	0.03%	o ¹³ C ₄
Isotopic Purity and Distribution by LC/MS SIM Analysis	SP10-0107	0.01%	/o ¹³ C ₁	2.03%	o ¹³ C ₅
		0.00%	∕₀ ¹³ C ₂	97.91%	∕₀ ¹³ C ₆
		0.01%	∕₀ ¹³ C ₃		
Identity by ¹ H-NMR Analysis	USP <761>, SP10-0116	Con	sistent wit	h Struc	ture
Residual Solvent Analysis by GC/FID Headspace	AM1087 ²		0.310	%	
Residual Water Analysis by Karl Fischer Coulometry	AM1346 ²	Belc	ow Quantit	ation Li	mit
Inorganic Content by Microash Analysis	SP10-0135	I	< 0.2	%	
		· '	Calculate	d Ana	alyzed
Elemental Analysis	Outcoursed	С	41.94%	59	.77%
	Outsourceu	н	6.79%	6.	65%
		N	6.99%	7.	08%
Mass Balance Purity Factor 98.40%					

 1 0.03% Norfentanyl- $^{13}C_{6}$ was 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:	Asc	entis Exp	oress C1	8, 2.7 µ	m,
	3.0	x 100 m	m		
Mobile Phase	: A:	Acetonit	rile		
	В:	0.1% Ph	osphorio	c acid in	Water
Gradient:	Tim	ie (min)	% A	% B	
		0.0	10	90	
		8.0	70	30	
		10.0	70	30	
		10.1	10	90	
Flow Rate:	0.7	mL/min			
Wavelength:	210) nm			
Sample Name	FC:	10291801	_		
Acquired:	Feb	oruary 06	, 2019		
Peak # F	Ret Time	e A	rea %		
1	2.48		0.03		
2	3.40		98.64		
3	3.64		0.63		
4	3.74		0.04		
5	3.89		0.05		
6	4.05		0.02		
7	4.21		0.21		
8	4.33		0.02		
9	4.38		0.05		
10	4.54		0.01		
11	4.59		0.13		
12	4.77		0.03		
13	4.92		0.02		
14	5.47		0.02		
15	5.72		0.02		
16	5.90		0.01		
17	7.02		0.02		
18	7.27		0.04		

Peak #1 has been identified as Norfentanyl-¹³C₆.

GC/FID



Column:	DB-35r	ns, 30 m x 0.53 m	m ID,
Temp Progr Injector Te Detector Te	1.0 μm film thicknessTemp Program:1.0 μm film thickness40°C to 200°C at 40°C/mir 200°C to 300°C at 5°C/mir hold 16 minInjector Temp:Cool-on-ColumnDetector Temp:325°C		in in
Sample Nai Acquired:	me: FC1029 January	91801 / 31, 2019	
Peak #	Ret Time	Area %	
1	4.08	0.01	
2	17.41	0.05	
3	24.91	98.88	
4	25.51	0.91	
5	26.05	0.16	

Residual Solvent Analysis by GC/FID Headspace



Column	:	DB-ALC1 30 m	n x 0.53 mm,	
Temp Pi	rogram:	40°C hold 12 i 40°C/min hold	min to 220°C at	
Carrier	Gas:	Helium		
Flow Ra	te:	2.0 mL/min		
Detecto	r Heater Temp:	250°C		
Injector	:	Headspace Sa	mpler	
HS Oven Temp:		60°C		
Vial Equilibration:		10 minutes		
Sample	Name:	FC10291801		
Acquire	d:	January 23, 20)19	
Peak	Compound	Area	Weight %	
1	Ethanol	28.36	0.24	
2	Ethyl Ether	179.25	0.08	
3	NMP	NA	NA	
Total			0.31	





Isotopic Purity by LC/MS



Stability

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

Short Term Stability: A summary of accelerated stability findings for a related product (H-130-0.5ML, (±)-beta-Hydroxythiofentanyl 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 (Shinning, Stability studies support the transport of this product at ambient conditions			

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 20 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 14, 2019	Initial version.
01	April 03, 2019	Corrected the product number in the footer of the certificate.
02 April 17, 2020	April 17 2020	Updated Retest Date of May 2020 to February 2021.
	Added Long Term Stability data.	
03	December 04, 2020	Updated Retest Date of February 2021 to November 2021.



Certified Reference Material - Certificate of Analysis

Methoxyacetyl fentanyl, Primary Measurement Standard

2-Met	hoxy-N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl] acetamine HCl Cerilliant Quality	
Product No.:	M-220-1ML ISO 17034	
Lot No.:	FC01031901	
Description of CRM:	Methoxyacetyl fentanyl HCl in Methanol (Solution)	
	Nominal concentration is adjusted for HCl content.	
Potost Dato:	December 2021 See Section "Stability Assessment" ISO 14001	
Relest Date.		
Storage:	Store unopened in freezer (-10 °C to -25 °C).	
Shipping:	Ambient. See Section "Stability Assessment".	
Chemical formula:	$C_{22}H_{28}N_2O_2 \bullet HCI$	
CAS No.:	101365-54-2	
Regulatory:	USDEA Schedule I	

Analyte	Certified Concentration \pm associated uncertainty U, $u=k*u$ (k=2)
Methoxyacetyl fentanyl	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.



Darron Ellsworth, Quality Assurance Manager

December 30, 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 calcuated based on: the actual mass; Mass balance purity factor of the analyte(s); measured mass of the solution; and the density of the pure diluent at 20°C.
- Fill volume is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- Concentration is verified against an independently prepared calibration solution gravimetrically prepared.
- Additional certification information available upon request.

Solution Standard Verification

New Lot

FC01031901

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	8 2 7 um 3 0 x 100 mm	Calibration	Curve: Points:	Linear Regression
Mohile Phase	Ascentis Express C18, 2.7 µm, 3.0 x 100 mm		Linearity (r) ·	4
Flow Rate:	(25:75) 1.5 mL/min		Linearity (I).	1.000
Wavelength:	210 nm				
		Verified Concentration	n (mg/mL)	%F	RSD - Homogeneity
Standard Solution	Lot Number	Actual Result	ts		Actual Results

• 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.

0.996

0.7

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:	Methoxyacetyl fentanyl HCl FC10161802 C ₂₂ H ₂₈ N ₂ O ₂ • HCl 101365-54-2	Molecular Weig Molecular Weig Salt Adjustmer	ght (base): 352.47 ght (salt): 388.93 nt: 1.103	
	Material Characte	erization Summary		
Analytical Test		Method	Results	
Primary Chromatographic Purity by HPLC/UV Analysis		SP10-0102	99.4% ¹	
Secondary Chromatographic Purity by GC/FID Analysis		SP10-0101	99.3% ²	
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 ³	0.53%	
Residual Water Analysis by Karl Fischer Coulometry		AM1346 ³	Below Quantitation Limit	
Inorganic Content by Microash Analysis		SP10-0135	< 0.2%	
Mass Balance Purity Factor			98.90%	

¹ 0.15% 4-ANPP detected by HPLC/UV analysis; no Fentanyl detected.

² 0.17% 4-ANPP detected by GC/FID analysis; no Fentanyl detected.

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:	Ascent	is Express Ph	enyl-He	xyl,
	2.7 µm	n, 3.0 x 100 r	nm	
Mobile Phase:	A: Ace	tonitrile		
	B: 0.10	% Phosphoric	c acid in	Water
Gradient:	Time (r	min) %A	% B	
	0.0	10	90	
	8.0	70	30	
	10.0) 70	30	
	10.1	1 10	90	
Flow Rate:	0.7 mL	/min		
Wavelength:	210 nn	า		
Sample Name:	FC1016	51802		
Acquired:	Februa	ry 07, 2019		
		• • • •		
Реак # К		Area %		
1	2.89	0.05		
2	3.36	0.01		
3	3.56	0.01		
4	3.65	99.45		
5	3.97	0.15		
6	4.11	0.02		
/	4.1/	0.02		
8	4.49	0.04		
9	4.56	0.01		
10	4 63	0.20		
11	4.05			
	4.85	0.00		
12	4.85 4.97	0.00 0.01		
12 13	4.85 4.97 5.40	0.00 0.01 0.03		

Peak 5 has been identified as 4-ANPP

GC/FID



Column:	DB-5m 1.5 μm 40°C to	s, 30 m x 0.53 mm ID, film thickness 9 200°C at 40°C/min	
Temp Program	n:		
	200°C		bia 16 min
Injector Temp	Cool-or	n-Column	
Detector Tem	p: 325°C		
Sample Name Acquired:	FC1016 Februar	51802 ry 12, 2019	
Peak # R	et Time	Area %	
1	10.66	0.07	
2	13.71	0.01	
3	15.75	0.17	
4	18.73	0.01	
5	21.08	99.30	
6	21.52	0.06	
7	21.64	0.04	
8	21.89	0.03	
9	22.38	0.02	
10	23.85	0.26	
11	26.29	0.02	
12	27.69	0.02	

Peak 3 has been identified as 4-ANPP

Residual Solvent Analysis by GC/FID Headspace



Instrument:

JEOL ECS 400

¹H NMR



Certficate Page 8 of 10





Stability

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

Short Term Stability: A summary of accelerated stability findings for 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 21 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 19, 2019	Initial version.
01	April 20, 2020	Revised Retest Date May 2020 to March 2021.
01 April 29, 2	April 29, 2020	Added Long Term Stability Section.
02	December 30, 2020	Revised Retest Date March 2021 to December 2021.



Certified Reference Material - Certificate of Analysis

Methoxyacetyl fentanyl-¹³C₆, Primary Measurement Standard

2	P-Methoxy-N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl] acetamine- ¹³ C ₆ HCl	Cerilliant Quality
Product No.:	M-221-1ML	150 17034
Lot No.:	FC01141901	130 17034
Description of	CRM: Methoxyacetyl fentanyl- ¹³ C ₆ HCl in Methanol (Solution)	ISO/IEC 17025
	Nominal concentration is adjusted for HCl content.	ISO 13485
Retest Date:	December 2021 See Section "Stability Assessment".	ISO 14001
Storage:	Store unopened in freezer (-10 °C to -25 °C).	ISO 9001
Shipping:	Ambient. See Section "Stability Assessment".	$\bigcap N \bigcap$
Chemical form	Ila: $C_{16}^{13}C_{6}H_{28}N_{2}O_{2} \bullet HCI$ $H_{3}CO_{4}$	
CAS No.:	NA *	
Regulatory:	USDEA Schedule I	*
		• HCI

Analyte		Certified Concentration \pm associated uncertainty U, $u=k*u$ (k=2)	
Methoxyacetyl fen	tanyl- ¹³ C ₆	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 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. Nominal concentration is adjusted for HCl 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 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.	



DER

December 30, 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 calcuated based on: the actual mass; Mass balance purity factor of the analyte(s); measured mass of the solution; and the density of the pure diluent at 20°C.
- Fill volume is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- Concentration is verified against an independently prepared calibration solution gravimetrically prepared.
- Additional certification information available upon request.

Solution Standard Verification

Concentration accuracy and within- and between-bottle homogeneity 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
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 (25:75)	Linearity (r) :	1.000
Flow Rate:	1.2 mL/min		
Wavelength:	210 nm		
	Verified Concentration	n (mg/mL)	%RSD - Homogeneity

		Vermed concentration (mg/me)	/oksb = nonogeneity
Standard Solution	Lot Number	Actual Results	Actual Results
New Lot	FC01141901	0.998	1.1

• 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 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:	Methoxyacetyl fentanyl- $^{13}C_6$ FC10311801 C ₁₆ $^{13}C_6H_{28}N_2O_2 \bullet HCl$ NA	, HCl Molecular Weig Molecular Weig Salt Adjustme	ght (base): ght (salt): nt:	358.43 394.89 1.102
	Material Charact	erization Summary		
Analytical Test		Method	Res	ults
Primary Chromatographic	Purity by HPLC/UV Analysis	SP10-0102	99	6%
Secondary Chromatograph	hic Purity by GC/FID Analysis	SP10-0101	99.	8%
Identity by LC/MS Analysi	S	SP10-0107	Consistent w	vith Structure
			0.00% 13	C ₀ vs ¹³ C ₆
			0.00% ¹³ C ₀	0.08% ¹³ C ₄
Isotopic Purity and Distrib	oution by LC/MS SIM Analysis	SP10-0107	0.00% ¹³ C ₁	4.07% ¹³ C ₅
			0.00% ¹³ C ₂	95.85% ¹³ C ₆
			0.00% ¹³ C ₃	
Identity by ¹ H-NMR Analy	sis	USP <761>, SP10-0116	Consistent w	vith Structure
Residual Solvent Analysis	by GC/FID Headspace	AM1087 ¹	0.14%	
Residual Water Analysis b	y Karl Fischer Coulometry	AM1346 ¹	Below Quan	titation Limit
Inorganic Content by Micr	oash Analysis	SP10-0135	< 0.2%	
Mass Balance Purity Facto	r		99.	50%

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	Ascentis Express C18, 2.7 µm,				
	3.0 x 100	mm				
Mobile Pha	se: A: Acetoni	trile				
	B: 0.1% P	hosphoric	acid in	Water		
Gradient:	Time (min))%A	% B			
	0.0	10	90	-		
	8.0	70	30			
	10.0	70	30			
	10.1	10	90			
Flow Rate:	0.7 mL/mi	n				
Wavelengtl	h: 210 nm					
-						
Sample Na	me: FC1031180	FC10311801				
Acquired:	February 2	February 25, 2019				
-	-					
Peak #	Ret Time	Area %				
1	3.00	0.01				
2	3.51	0.01				
3	3.84	99.57				
4	4.02	0.23				
5	4.13	0.03				
6	4.27	0.04				
7	4.45	0.01				
8	4.56	0.01				
9	4.62	0.01				

11

4.95

0.05

GC/FID



Column: Temp Prog	DB-5ms 1.5 µm ram: 40°C to	s, 30 m x 0.53 mm film thickness 200°C at 40°C/mir	[D
Injector Te	200°C t hold 16 emp: Cool-on	o 300°C at 5°C/mir min -Column	1
Detector I	emp: 325°C		
Sample Na	me: FC1031	1801	
Acquired:	Februar	y 25, 2019	
Peak #	Ret Time	Area %	
Peak #	Ret Time 10.66	Area % 0.02	
Peak # 1 2	Ret Time 10.66 15.75	Area % 0.02 0.10	
Peak # 1 2 3	Ret Time 10.66 15.75 18.72	Area % 0.02 0.10 0.01	
Peak # 1 2 3 4	Ret Time 10.66 15.75 18.72 20.10	Area % 0.02 0.10 0.01 0.01	
Peak # 1 2 3 4 5	Ret Time 10.66 15.75 18.72 20.10 21.10	Area % 0.02 0.10 0.01 0.01 99.76	
Peak # 1 2 3 4 5 6	Ret Time 10.66 15.75 18.72 20.10 21.10 21.87	Area % 0.02 0.10 0.01 0.01 99.76 0.02	
Peak # 1 2 3 4 5 6 7	Ret Time 10.66 15.75 18.72 20.10 21.10 21.87 22.25	Area % 0.02 0.10 0.01 0.01 99.76 0.02 0.01	

22.75

23.25

26.26

0.02

0.04

0.01

Residual Solvent Analysis by GC/FID Headspace



9

10 11

BQL - Below Quantitation Limit



LC/MS



Isotopic Purity by LC/MS SIM

Column:	Kinetex C18,	, 2.6 µn	n, 2.1 x 50 mm	Flow Rate:	0.5 mL/min
Mobile Phase:	A: 0.1% Formic acid in Water			Scan Range:	353-359 amu
	B: Acetonitri	le		Ionization:	Electrospray, Positive Ion
Gradient:	Time (min)	% A	% B	Instrument:	Agilent 6410A
	0.0	80	20		Mass Spectrometer
	5.0	20	80	Acquired:	February 26, 2019
	6.0	20	80		
	7.0	80	20		
	11.0	80	20		



Stability

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

Short Term Stability: A summary of accelerated stability findings for a related product (M-200-0.5ML, Methoxyacetyl fentanyl 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 21 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	00 March 22, 2019 Initial version.	
01	01 April 02, 2019 Revised Chemical Name Synonym.	
0.2	April 29, 2020	Revised Retest Date from May 2020 to March 2021.
02		Added Long Term Stability.
03	December 30, 2020	Revised Retest Date from March 2021 to December 2021.



Certified Reference Material - Certificate of Analysis

4'-Methyl acetyl fentanyl, Primary Measurement Standard

N-[1-[2-(4-methylphenyl)ethyl]-4-piperidinyl]-N-phenyl-acetamide HCl

Product No.:	M-223-1ML	ISO 17034
Lot No.:	FC01281901	
Description of CRM:	4'-Methyl acetyl fentanyl HCl in Methanol (Solution)	ISO/IEC 17025
•	Nominal concentration is adjusted for HCl content.	ISO 13485
Retest Date:	February 2022 See Stability Section	ISO 14001
Storage:	Store unopened in freezer (-10 °C to -25 °C).	ISO 9001
Shipping:	Ambient. See Stability Section HCI CH ₃	
Chemical formula:	C ₂₂ H ₂₈ N ₂ O•HCl	
CAS No.:	1071703-95-1 _{H3} с Ц _Ņ (
Regulatory:	USDEA Schedule I	

Analyte	Certified Concentration \pm associated uncertainty U, u=k*u (k=2)
4'-Methyl acetyl fentanyl	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 3.

Measurement method:	The certified value is calculated from high precision weighing of thoroughly characterized starting material. See "Details about certification process" on page 3.
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

March 05, 2021

Issue Date

Cerilliant Quality

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 calcuated based on: the actual mass; Mass balance purity factor of the analyte(s); measured mass of the solution; and the density of the pure diluent at 20°C.
- Fill volume is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- Concentration is verified against an independently prepared calibration solution gravimetrically prepared.
- Additional certification information available upon request.

Solution Standard Verification

Solution

Concentration accuracy and within- and between-bottle homogeneity areanalytically 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:	HPLC/UV		Calibration Curve:		Linear Regression
Column:	Ascentis Express C1	Number of I	Points:	4	
Mobile Phase:	Acetonitrile:0.1% P (30:70)	hosphoric acid in Water	Linearity (r)):	1.000
Flow Rate:	1.2 mL/min				
Wavelength:	210 nm				
		Verified Concentration	(mg/mL)	%F	SD - Homogeneity
Standard	Lot Number	Actual Result	s		Actual Results

New Lot		FC01281901	0.995	0.5		
٠	 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:	4'-Methyl acetyl fentanyl HC FC01111901 C ₂₂ H ₂₈ N ₂ O•HCl 1071703-95-1	Cl Molecular Weig Molecular Weig Salt Adjustmer	ght (base): 336.47 ght (salt): 372.93 nt: 1.108				
Material Characterization Summary							
Analytical Test		Method	Results				
Primary Chromatographic Purity by HPLC/UV Analysis		SP10-0102	99.5%				
Secondary Chromatographic Purity by GC/FID Analysis		SP10-0101	99.6%				
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	0.12%				
Residual Water Analysis by Karl Fischer Coulometry		AM1346 ¹	0.43%				
Inorganic Content by Microash Analysis		SP10-0135	< 0.2%				
Mass Balance Purity Factor			98.96%				

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 100	3.0 x 100 mm			
Mobile Pha	se: A: Acetor	A: Acetonitrile			
	B: 0.1%	B: 0.1% Phosphoric acid in Water			
Gradient:	Time (mi	n) %A	% B	_	
	0.0	10	90	-	
	8.0	70	30		
	10.0	70	30		
	10.1	10	90		
Flow Rate:	0.7 mL/n	0.7 mL/min			
Wavelengt	h: 210 nm	210 nm			
Sample Na	me: FC01111	FC01111901			
Acquired:	March 04	March 04, 2019			
Peak #	Ret Time	Area %			
1	2.89	0.01			
2	3.81	0.23			
3	4.44	99.47			
4	4.64	0.25			
5	4.78	0.01			
6	4.95	0.02			

0.02

GC/FID



Column:	DB-5ms, 30 m x 0.53 mm ID,			
Tomp Brogram	1.5 μm	1.5 μ m film thickness		
remp Program.	200°C t	200°C to 300°C at 5°C/min		
	hold 16	min		
Injector Temp:	Cool-on	Cool-on-Column		
Detector Temp:	325°C	325°C		
Sample Name:	FC0111	FC01111901		
Acquired:	March C	March 05, 2019		
Peak # Ret	Time	Area %		
1 Q	05			
2 1	7 20	0.18		
3 2() 15	99 59		
5 20				

5.11

7



Residual Solvent Analysis by GC/FID Headspace

⁺H NMR


LC/MS

Column	1:	Ascent	is Expr	ess C1	8, 2.7	μm,		Flo	w Rate:	0.4 mL/n	nin	
		3.0 x 5	50 mm					Sca	n Range:	100-1200) amu	
Mobile	Phase:	A: 0.19	% Forr	nic acio	d in Wa	ter		Ion	ization:	Electrosp	ray, Positive	Ion
		B: Ace	tonitril	e				Ins	trument:	Waters X	EVO G2 QTC)F
Gradier	nt:	Time (min)	% A	% B	_		Acc	uired:	March 04	, 2019	
		0.	0	80	20							
		0.	5	80	20							
		4.	0	20	80							
		5.3	8	20	80							
		6.	0	80	20							
		8.	0	80	20							
RMM-22	6 FC01111901				4'-	Methyl ace	yl fentanyl H			Cone V	oltage: 25.000	00000
W030419	21 444 (1.681) Cr	n (443:448)									1: TOF MS	S ES+
100-		337.2	286									2.32e7
-				Theore	tical [N	1 + H]+: 3	337.2280					
-				Found	[M + F	1]+: 337.2	286					
<u></u>												
0` _		3	38.2312									
-		Í										
-		326.2328	39.2339									
0												⊢ m/z
100	200	300	400		500	600	700	800	900	1000	1100	

Stability

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

Short Term Stability: A summary of accelerated stability findings for 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 23 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 29, 2019	Initial version.
01	May 10, 2019	Updated Short Term Stability to include four week stability data.
02	May 04 2020	Revised Retest Date May 2020 to April 2021.
	May 04, 2020	Added Long Term Stability Section.
03	March 05, 2021	Revised Retest Date April 2021 to February 2022.



Certified Reference Material - Certificate of Analysis

4'-Methyl acetyl fentanyl-¹³C₆, Primary Measurement Standard

٨	-[1-[2-(4-methylphenyl)ethyl]-4-piperidinyl]-N-phenyl-acetamide- ¹³ C ₆ HCl	Cerilliant Quality
Product No.:	M-224-1ML	ISO 17034
Description of C	RM: 4'-Methyl acetyl fentanyl- $^{13}C_6$ HCl in Methanol (Solution)	ISO/IEC 17025
-	Nominal concentration is adjusted for HCl content.	ISO 13485
Retest Date:	February 2022 See Stability Section	ISO 14001
Storage:	Store unopened in freezer (-10 °C to -25 °C).	ISO 9001
Shipping:	Ambient. See Stability Section	HCI CH ₃
Chemical formu	la: C ₁₆ ¹³ C ₆ H ₂₈ N ₂ O•HCl	Ņ
CAS No.:	NA н ₃ с ¹ м	J
Regulatory:	USDEA Schedule I	

Analyte	Certified Concentration \pm associated uncertainty U, u=k*u (k=2)
4'-Methyl acetyl fentanyl- ¹³ C 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 3.

Measurement method:	The certified value is calculated from high precision weighing of thoroughly characterized starting material. See "Details about certification process" on page 3.
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. 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.



March 05, 2021

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

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 calcuated based on: the actual mass; Mass balance purity factor of the analyte(s); measured mass of the solution; and the density of the pure diluent at 20°C.
- Fill volume is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- Concentration is verified against an independently prepared calibration solution gravimetrically prepared.
- Additional certification information available upon request.

Solution Standard Verification

Solution

Concentration accuracy and within- and between-bottle homogeneity areanalytically 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	
Column:	Ascentis Express C1	Number of Points: 4		4		
Mobile Phase:	Acetonitrile:0.1% P (30:70)	hosphoric acid in Water	Linearity (r):	1.000	
Flow Rate:	1.3 mL/min					
Wavelength:	210 nm					
		Verified Concentration	(mg/mL)	%F	RSD - Homogeneity	
Standard	Lot Number	Actual Result	s		Actual Results	

New Lot FC01241902		FC01241902	1.006	1.8		
٠	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:	4'-Methyl acetyl fentanyl- ¹³	C ₆ HCl Molecular Weig	ght (base):	342.43	
Chemical Formula:	$C_{16}^{13}C_{6}H_{28}N_{2}O\bullet HCI$	Salt Adjustme	Salt Adjustment:		
CAS Number:	NA				
	Material Characte	erization Summary			
Analytical Test		Method	Results		
Primary Chromatographic	Purity by HPLC/UV Analysis	SP10-0102	99	99.5%	
Secondary Chromatograph	nic Purity by GC/FID Analysis	SP10-0101	99	.7%	
Identity by LC/MS Analysis	s	SP10-0107	Consistent v	vith Structure	
			0.00% 13	C ₀ vs ¹³ C ₆	
			0.00% ¹³ C ₀	0.08% ¹³ C ₄	
Isotopic Purity and Distrib	ution by LC/MS SIM Analysis	SP10-0107	0.00% ¹³ C ₁	4.08% ¹³ C ₅	
			0.00% ¹³ C ₂	95.85% ¹³ C ₆	
			0.00% ¹³ C ₃		
Identity by ¹ H-NMR Analys	sis	USP <761>, SP10-0116	Consistent with Structure		
Residual Solvent Analysis	by GC/FID Headspace	AM1087 ¹	None Detected		
Residual Water Analysis b	y Karl Fischer Coulometry	AM1346 ¹	Below Quan	titation Limit	
Inorganic Content by Micro	oash Analysis	SP10-0135	< 0.2%		
Mass Balance Purity Facto	r		99.	48%	

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	s Express C1	.8, 2.7 µr	n,
	3.0 x 1	00 mm		
Mobile Pha	se: A: Acet	onitrile		
	B: 0.19	% Phosphoric	acid in V	Vater
Gradient:	Time (r	nin) %A	% B	
	0.0	10	90	
	8.0	70	30	
	10.0) 70	30	
	10.1	10	90	
Flow Rate:	0.7 mL	/min		
Wavelengt	h: 210 nm	ı		
	500111	1000		
Sample Na	me: FCUIII	1903		
Acquirea:	Februa	ry 26, 2019		
Peak #	Ret Time	Area %		
1	0.55	0.01		
2	1.77	0.01		
3	3.15	0.01		
4	3.55	0.01		
5	3.60	0.01		
6	3.76	0.00		
7	4.00	0.01		
8	4.17	0.01		
9	4.21	0.00		
10	4.46	99.44		
11	4.67	0.16		
12	4.82	0.04		
13	4.88	0.01		
14	5.00	0.02		
15	5.04	0.02		
16	5.16	0.03		
17	5.32	0.03		
18	5.50	0.16		
19	6.82	0.01		

GC/FID



Co	lumn:	DB-5	ns, 30 m x 0.53 mm ID	,
Те	mp Progra	1.5 μ am: 40°C 200°C hold 2	n film thickness to 200°C at 40°C/min C to 300°C at 5°C/min L6 min	
Inj	jector Ten	np: Cool-	on-Column	
De	tector Ter	np: 325°0	2	
Sa Ac	mple Nam quired:	FC01: Febru	L11903 ary 26, 2019	
P	eak #	Ret Time	Area %	
	1	4.22	0.01	
	2	4.44	0.01	
	-	17 00	0.06	
	3	17.20	0.06	
	3 4	17.20 20.15	99.73	
	3 4 5	20.15 20.96	0.08 99.73 0.01	
	3 4 5 6	20.15 20.96 21.36	0.08 99.73 0.01 0.02	
	3 4 5 6 7	17.20 20.15 20.96 21.36 21.77	0.06 99.73 0.01 0.02 0.01	
	3 4 5 6 7 8	17.20 20.15 20.96 21.36 21.77 21.95	0.06 99.73 0.01 0.02 0.01 0.03	
	3 4 5 6 7 8 9	17.20 20.15 20.96 21.36 21.77 21.95 22.41	0.06 99.73 0.01 0.02 0.01 0.03 0.12	
	3 4 5 6 7 8 9 10	17.20 20.15 20.96 21.36 21.77 21.95 22.41 22.92	99.73 0.01 0.02 0.01 0.03 0.12 0.00	

Residual Solvent Analysis by GC/FID Headspace

FID1 A. (F-002-42-RMM-227 FC01111903 9.81mg.D)	Column:		DB-ALC1 30 m x 0.	53 mm,
Norm. 500-	Temp Pr	ogram:	3 µm film thickness 40°C hold 12 min t 40°C/min hold 5.5	s o 220°C at min
	Carrier G	Gas:	Helium	
400 -	Flow Rat	te:	2.0 mL/min	
	Detector	• Heater Temp:	250°C	
-	Injector	:	Headspace Sample	r
300 -	HS Oven	Temp:	60°C	
	Vial Equi	ilibration:	10 minutes	
200-	Sample I	Name:	FC01111903	
	Acquired	1:	February 26, 2019	
100-	Peak	Compound	Area	Weight %
	1	NMP	NA	NA
0-	Total			ND
0 25 5 7,5 10 125 15 17,5 20 min			ND - None Det	ected



LC/MS



Isotopic Purity by LC/MS SIM

Column:	Kinetex C18,	, 2.6 µn	n, 2.1 x 50 mm	Flow Rate:	0.5 mL/min
Mobile Phase:	A: 0.1% For	mic acio	d in Water	Scan Range:	337-343 amu
	B: Acetonitri	le		Ionization:	Electrospray, Positive Ion
Gradient:	Time (min)	% A	% B	Instrument:	Agilent 6410A
	0.0	80	20		Mass Spectrometer
	5.0	20	80	Acquired:	February 26, 2019
	6.0	20	80		
	7.0	80	20		
	11.0	80	20		



Stability

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

Short Term Stability: A summary of accelerated stability findings for a related product (M-223-1ML, 4'-Methyl acetyl fentanyl 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 23 months has been established for a related product (M-223-1ML, 4'-Methyl acetyl fentanyl HCl) 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 29, 2019	Initial version.
01	May 10, 2019	Updated Short Term Stability to include four week stability data.
02 May 04 2020	Revised Retest Date May 2020 to April 2021.	
02	May 04, 2020	Added Long Term Stability Section.
03	March 05, 2021	Revised Retest Date of April 2021 to February 2022.



Certified Reference Material - Certificate of Analysis

Remifentanil, Primary Measurement Standard

3-[Methoxycarbonyl-4-[(1-oxopropyl)phenylamino]1-piperidine]propanoic acid methyl ester HCl

Product No.:	R-032-1ML	Cerilliant Quality
Lot No.:	FC01141905	ISO 17034
Description of CRM:	Remifentanil HCI in Methanol (Solution) Nominal concentration is adjusted for HCI content.	ISO/IEC 17025
Retest Date:	February 2022 See Section "Stability Assessment".	ISO 13485
Storage:	Store unopened in freezer (-10 °C to -25 °C).	ISO 14001
Shipping:	Ship cold. See Section "Stability Assessment". $\circ \gamma^{\text{OCH}_3}$	ISO 9001
Chemical formula:	C ₂₀ H ₂₈ N ₂ O ₅ • HCl	
CAS No.:	132539-07-2	
Regulatory:	USDEA Schedule II	

Analyte		Certified Concentration \pm associated uncertainty U, $u=k*u$ (k=2)		
Remifentar	nil	1.000 ± 0.006 mg/mL		
Metrological traceability:	Traceable to the S unbroken chain of page 3.	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 3.	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:	Concentration is of solvents and resid Users should quar laboratory practic concentration. Eac Nominal concentration before use.	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. ation is adjusted for HCl content. No adjustment required		
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 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.		



Darron Ellsworth, Quality Assurance Manager

March 02, 2021

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 calcuated based on: the actual mass; Mass balance purity factor of the analyte(s); measured mass of the solution; and the density of the pure diluent at 20°C.
- Fill volume is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- Concentration is verified against an independently prepared calibration solution gravimetrically prepared.
- Additional certification information available upon request.

Solution Standard Verification

Concentration accuracy and within- and between-bottle homogeneity 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
Column:	Ascentis Express C1	18, 2.7 μm, 3.0 x 100 mm	Number of	Points:	4
Mobile Phase:	Acetonitrile:0.1% P (30:70)	hosphoric acid in Water	Linearity (r):	1.000
Flow Rate:	1.5 mL/min				
Wavelength:	210 nm				
		Verified Concentration	(mg/mL)	%F	RSD - Homogeneity

Standard Solution	Lot Number	Actual Results	Actual Results
New Lot	FC01141905	0.996	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:	Remifentanil HCl FC09271801 $C_{20}H_{28}N_2O_5 \bullet HCl$ 132539-07-2	Molecular Weig Molecular Weig Salt Adjustmer	ght (base): 376.45 ght (salt): 412.91 nt: 1.097	
	Material Characte	erization Summary		
Analytical Test		Method	Results	
Primary Chromatographic	Purity by HPLC/UV Analysis	SP10-0102	99.8% ¹	
Secondary Chromatographic Purity by GC/FID Analysis		SP10-0101	99.7%	
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 ²	0.93%	
Residual Water Analysis by Karl Fischer Coulometry		AM1346 ²	Not Detected	
Inorganic Content by Microash Analysis		SP10-0135	< 0.2%	
Mass Balance Purity Facto	r		98.90%	

¹ 0.02% Remifentanil acid 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 I	Express C	ا 18, 2.7	um,
	3.0 x 100	mm		
Mobile Pha	se: A: Aceton	itrile		
	B: 0.1% I	Phosphoric	c acid in	Water
Gradient:	Time (mir	n) % A	% B	_
	0.0	10	90	-
	8.0	70	30	
	10.0	70	30	
	10.1	10	90	
Flow Rate:	0.7 mL/m	nin		
Wavelengt	h: 210 nm			
-				
Sample Na	me: FC092718	301		
Acquired:	February	28, 2019		
-	,			
Peak #	Ret Time	Area %		
1	2.38	0.01		
2	3.01	0.04		
3	3.30	0.02		
4	3.52	99.78		
5	3.98	0.01		
6	4.14	0.09		
7	4.40	0.01		
8	4.72	0.03		
8 9	4.72 4.84	0.03 0.01		

Peak #3 has been identified as Remifentanil acid

GC/FID



Column:	DB-5m:	s, 30 m x 0.53 mm II film thicknoss	C
Temp Prog	ram: 40°C to	240°C at 40°C/min	
	240°C 1	to 300°C at 5°C/min	
	hold 20	min	
Injector Te	emp: Cool-or	n-Column	
Detector T	emp: 325°C		
Commission No.		1001	
Sample Na	me: FC0927	1801	
Acquired:	March	5, 2019	
Peak #	Ret Time	Area %	
Peak # 1	Ret Time 7.92	Area % 0.10	
Peak # 1 2	Ret Time 7.92 8.55	Area % 0.10 0.00	
Peak # 1 2 3	Ret Time 7.92 8.55 9.97	Area % 0.10 0.00 0.00	
Peak # 1 2 3 4	Ret Time 7.92 8.55 9.97 10.78	Area % 0.10 0.00 0.00 0.02	
Peak # 1 2 3 4 5	Ret Time 7.92 8.55 9.97 10.78 11.38	Area % 0.10 0.00 0.00 0.02 0.03	
Peak # 1 2 3 4 5 6	Ret Time 7.92 8.55 9.97 10.78 11.38 11.55	Area % 0.10 0.00 0.00 0.02 0.03 99.73	
Peak # 1 2 3 4 5 6 7	Ret Time 7.92 8.55 9.97 10.78 11.38 11.55 11.97	Area % 0.10 0.00 0.00 0.02 0.03 99.73 0.01	
Peak # 1 2 3 4 5 6 7 8	Ret Time 7.92 8.55 9.97 10.78 11.38 11.55 11.97 12.21	Area % 0.10 0.00 0.00 0.02 0.03 99.73 0.01 0.01	
Peak # 1 2 3 4 5 6 7 8 9	Ret Time 7.92 8.55 9.97 10.78 11.38 11.55 11.97 12.21 12.56	Area % 0.10 0.00 0.02 0.03 99.73 0.01 0.01 0.01	

Residual Solvent Analysis by GC/FID Headspace



Column:		DB-ALC1 30 m	x 0.53 mm,	
		3 µm film thickness		
Temp Pro	gram:	40°C hold 12 m	in to 220°C at	
		40°C/min hold	5.5 min	
Carrier Ga	as:	Helium		
Flow Rate	:	2.0 mL/min		
Detector	Heater Temp:	250°C		
Injector:		Headspace Sampler		
HS Oven Temp:		60°C		
Vial Equilibration:		10 minutes		
Sample Name:		FC09271801		
Acquired:		February 28, 20)19	
Peak	Compound	Area	Weight %	
1	Methanol	147.35	0.93	
2	NMP	NA	NA	
Total			0.93	







Stability

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

Short Term Stability: A summary of accelerated stability findings for this product is listed below.

Storage Condition	Mean Kinetic Temperature (MKT)	Time Period/Result
Freezer	-15°C	0.12% decrease in purity was noted after four weeks.
Refrigerator	4°C	0.23% decrease in purity was noted after four weeks.
Room Temperature	21°C	1.01% decrease in purity was noted after two weeks.
40°C	40°C	3.39% decrease in purity was noted after one week.
Transport/Shipping: Ship cold.		

Long Term Stability: Long term stability has been assessed for Freezer storage (-10 °C to -25 °C) conditions. Stability of a minimum of 23 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 25, 2019	Initial version.
01	April 24, 2020	Updated Retest Date of May 2020 to March 2021.
		Added Long Term Stability section.
02 March 02	March 02 2021	Updated Retest Date of March 2021 to February 2022.
02	March 02, 2021	Update page reference on first page.



Certified Reference Material - Certificate of Analysis

Remifentanil-¹³C₆, Primary Measurement Standard

 $3-[Methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-1-piperidine] propanoic acid methyl ester-{}^{13}C_{6} HCl$

Product No.:	R-033-1ML	Cerilliant Quality
Lot No.:	FC01141906	150 17034
Description of CRM:	Remifentanil- ¹³ C ₆ HCl in Methanol (Solution)	130 17034
	Nominal concentration is adjusted for HCl content.	ISO/IEC 1/025
Potost Dato:	February 2022 Soo Section "Stability Accossment"	ISO 13485
	Chara unananad in fragmer (10.90 to 20.00)	ISO 14001
Storage:	Store unopened in freezer (-10 °C to -25 °C). O_{CH_3}	
Shipping:	Ship cold. See Section "Stability Assessment".	ISO 9001
Chemical formula:	$C_{14}^{13}C_6H_{28}N_2O_5\bullet HCI$	
CAS No.:	NA * OCH2	
Regulatory:	USDEA Schedule II	
	CNO CH3	

Analyte		Certified Concentration ± associated uncertainty U, u=k*u (k=2)	
Remifentanil	⁻¹³ C ₆	1.000 ± 0.006 mg/mL	
Metrological traceability:	Traceable to the S unbroken chain of page 3.	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 3.	The certified value is calculated from high precision weighing of thoroughly characterized starting material. See "Details about certification process" on page 3.	
Intended use:	This Certified Refe calibration, and quapplications. 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 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. 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 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

March 02, 2021

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 calcuated based on: the actual mass; Mass balance purity factor of the analyte(s); measured mass of the solution; and the density of the pure diluent at 20°C.
- Fill volume is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- Concentration is verified against an independently prepared calibration solution gravimetrically prepared.
- Additional certification information available upon request.

Solution Standard Verification

Concentration accuracy and within- and between-bottle homogeneity 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 Cu	ırve
Analysis Method:	HPLC/UV	Calibration Cu	Irve: Linear Regression
Column:	Ascentis Express C18, 2.7 µm, 3.0 x 100 mm	Number of Poi	ints: 4
Mobile Phase:	Acetonitrile:0.1% Phosphoric acid in Water (30:70)	Linearity (r) :	1.000
Flow Rate:	1.5 mL/min		
Wavelength:	210 nm		
	Verified Concentratior	(mg/mL)	%RSD - Homogeneity

		Verified Concentration (ing/ine)	/iter nonogenercy
Standard Solution	Lot Number	Actual Results	Actual Results
New Lot	FC01141906	1.000	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 and salt adjustment are utilized to calculate the weighing adjustment necessary to ensure accuracy of the solution standard concentration.

Material Name: Remifentanil- ¹³ C ₆ HCl		Molecular Weight (base):		382.40
Material Lot: FC10031804		Molecular Weight (salt):		418.86
Chemical Formula:	$C_{14}^{13}C_{6}H_{28}N_{2}O_{5}\bullet HCI$	Salt Adjustme	nt:	1.095
CAS Number:	NA			
	Material Charact	erization Summary		
Analytical Test		Method	Res	sults
Primary Chromatographic	Purity by HPLC/UV Analysis	SP10-0102	99	.5%
Secondary Chromatograph	nic Purity by LC/MS Analysis	SP10-0107	> 99	9.9%
Identity by LC/MS Analysis	S	SP10-0107	Consistent with Structure	
			0.01% 13	C ₀ vs ¹³ C ₆
			0.01% ¹³ C ₀	0.09% ¹³ C ₄
Isotopic Purity and Distrib	ution by LC/MS SIM Analysis	SP10-0107	0.05% ¹³ C ₁	4.33% ¹³ C ₅
			0.02% ¹³ C ₂	95.49% ¹³ C ₆
			0.01% ¹³ C ₃	
Identity by ¹ H-NMR Analysis		USP <761>, SP10-0116	Consistent with Structure	
Residual Solvent Analysis by GC/FID Headspace		AM1087 ¹	0.93%	
Residual Water Analysis by Karl Fischer Coulometry		AM1346 ¹	0.23%	
Inorganic Content by Microash Analysis		SP10-0135	< 0.2%	
Mass Balance Purity Factor			98.	33%

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 3.0 x 1	s Express C1 00 mm	L8, 2.7 բ	ım,
Mohile Pha	se: A: Acet	onitrile		
	B: 0.19	6 Phosphoric	acid in	Water
Gradient:	Time (n	nin) %A	% B	mater
	0.0	10	90	
	8.0	70	30	
	10.0	70	30	
	10.1	10	90	
Flow Rate:	0.7 mL	/min		
Wavelength	1: 210 nm	1		
Sample Nar	ne: FC1003	1804		
Acquired:	March ()1, 2019		
Peak #	Ret Time	Area %		
1	2.93	0.01		
2	3.16	0.01		
3	3.30	0.01		
4	3.52	99.45		
5	3.92	0.01		
6	4.00	0.02		
7	4.09	0.06		
8	4.15	0.23		
9	4.21	0.02		
10	4.49	0.01		
11	4.54	0.01		
12	4.67	0.01		
13	4.73	0.09		
14	4.87	0.03		
14 15	4.87 4.95	0.03 0.01		



Residual Solvent Analysis by GC/FID Headspace





LC/MS



Isotopic Purity by LC/MS SIM



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

Short Term Stability: A summary of accelerated stability findings for a related product (R-024, Remifentanil HCl) is listed below.

Storage Condition	Mean Kinetic Temperature (MKT)	Time Period/Result	
Freezer	-15°C	No decrease in purity was noted afte	
Refrigerator	4°C	four weeks.	
Room Temperature	21°C	1.01% decrease in purity was noted after two weeks.	
40°C	40°C	3.39% decrease in purity was noted after one week.	
Transport/Shipping:	Ship cold.		
Long Term Stability:	Long term stability has been assessed for	Freezer storage (-10 °C to -25 °C)	

conditions. Stability of a minimum of 23 months has been established for a related product (R-032, Remifentanil HCl) 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 22, 2019	Initial version.
01	April 24, 2020	Updated Retest Date of May 2020 to March 2021.
		Added Long Term Stability section.
02	March 02, 2021	Updated Retest Date of March 2021 to February 2022.
		Update page reference on first page.



Certified Reference Material - Certificate of Analysis

U-47700-¹³C₃,¹⁵N₂, Primary Measurement Standard

(±)-trans-3,4-Dichloro-N-[2-(dimethylamino)cyclohexyl]-N-methyl-benzamide- ${}^{13}C_3$, ${}^{15}N_2$

		Cerimani Quany
Product No.:	U-013-1ML	ISO 17034
Lot No.:	FC12261802	100 17004
Description of CRM:	U-47700- $^{13}C_{31}^{15}N_{2}$ in Methanol (Solution)	ISO/IEC 17025
Retest Date:	January 2022 See Section "Stability Assessment".	ISO 13485
Storage:	Store unopened in freezer (-10 °C to -25 °C).	ISO 14001
Shipping:	Ship cold. See Section "Stability Assessment".	ISO 9001
Chemical formula:	$C_{13}^{13}C_{3}H_{22}^{15}N_{2}OCI_{2}$	
CAS No.:		
Regulatory:	USDEA Schedule I	H ₃

Analyte	Certified Concentration \pm associated uncertainty U, $u=k*u$ (k=2)
U-47700- ¹³ C ₃ , ¹⁵ N ₂	1.000 ± 0.006 mg/mL

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

Measurement method:	The certified value is calculated from high precision weighing of thoroughly characterized starting material. See "Details about certification process" on page 2.
Intended use:	This Certified Reference Material is suitable for the in vitro identification, calibration, and quantification of the analyte(s) in analytical and R&D applications. Not suitable for human or animal consumption.
Minimum sample size:	1 μL for quantitative applications
Instructions for handling and correct use:	Concentration is corrected for chromatographic purity, residual solvents and residual inorganics. No adjustment required before use. Users should quantitatively transfer desired volume using established good laboratory practices to spike into matrix or to dilute to the desired concentration. Each ampoule is intended for one-time use. 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 02, 2021

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 calcuated based on: the actual mass; Mass balance purity factor of the analyte(s); measured mass of the solution; and the density of the pure diluent at 20°C.
- Fill volume is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- Concentration is verified against an independently prepared calibration solution gravimetrically prepared.
- Additional certification information available upon request.
Solution Standard Verification

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

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 (35:65)	Linearity (r):	1.000
Flow Rate:	1.5 mL/min		
Wavelength:	220 nm		
	Verified Concentration	$\frac{1}{2}$	

		Vermed Concentration (ing/inc)	%KSD - Holliogeneity
Standard Solution	Lot Number	Actual Results	Actual Results
New Lot	FC12261802	0.993	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:	U-47700- ¹³ C ₃ , ¹⁵ N ₂ FC10111801	Chemical Forr CAS Number: Molecular We	mula: C ₁₃ ¹ NA ight: 334	³ C ₃ H ₂₂ ¹⁵ N ₂ OCl ₂ .23
	Material Characte	erization Summary		
Analytical Test		Method	Res	ults
Primary Chromatographi	ic Purity by HPLC/UV Analysis	SP10-0102	99.3	8%
Secondary Chromatogra	phic Purity by GC/FID Analysis	SP10-0101	99.8	8%
Identity by LC/MS Analysis		SP10-0107	Consistent with Structure	
			0.01% N	1 ₀ vs M ₅
Isotopic Purity and Distr	ibution by LC/MS SIM Analysis	SP10-0107	0.01% M_0 to M_2	2.61% M ₄
			0.03% M ₃	97.34% M ₅
Identity by ¹ H-NMR Anal	iysis	USP <761>, SP10-0116	Consistent w	ith 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			99.7	'9%

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:	Ase	centis Ex	press P	henyl-He	xyl,
Mobile Pha	ase: A: B:	Acetonit	rile	ric acid in	Water
Gradient:	Tim	ne (min)	% A	% B	
		0.0	10	90	
		8.0	80	20	
		10.0	80	20	
		10.1	10	90	
Flow Rate:	. 0.7	⁷ mL/min			
Wavelengt	: h: 22	0 nm			
Sample Na	me: FC	1011180	1		
Acquired:	Jar	nuary 14,	2019		
Peak #	Ret Time	e Are	ea %		
1	3.61	0	.00		
2	3.74	99	9.82		
3	3.98	0	.11		

GC/FID



Column: Temp Prog	DB-35 1.0 µr Jram: 40°C	ims, 30 m x 0.53 mm ID, n film thickness to 200°C at 40°C/min
Injector Te	200°C 200°C 200°C	to 280°C at 5°C/min hold 18 mir on-Column
Detector T	emp: 325°C	
Sample Na	me: FC101	.11801 rv 14 - 2019
Acquircui	Junua	, , , , 2015
Peak #	Ret Time	Area %
1	3.59	0.00
2	4.69	0.01
3	6.71	0.00
4	7.03	0.02
5	7.55	0.08
6	8.18	0.00

0.03

0.01

0.01

99.80

0.05

0.06

7

8

9

10

11

4

4.08

9.08

14.21

16.06

16.34

18.14

Residual Solvent Analysis by GC/FID Headspace



Instrument: JEOL ECS 400

¹H NMR



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





Isotopic Purity by LC/MS SIM



Stability

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

Short Term Stability: A summary of accelerated stability findings for a related product (U-003-1ML, U-47700) 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	1.58% decrease in purity was noted after two weeks.			
Transport/Shipping:	Ship cold.				

Long Term Stability: Long term stability has been assessed for Freezer storage (-10 °C to -25 °C) conditions. Stability of a minimum of 23 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, 2019	Initial version.
01 March 21 2020		Revised Retest Date from April 2020 to February 2021.
01	March 51, 2020	Added Long Term Stability section.
02	February 02, 2021	Revised Retest Date from February 2021 to January 2022.



Certified Reference Material - Certificate of Analysis

Vale	ryl fentanyl, Primary Measurement Standard	Cerilliant Quality
Ι	-Phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]-pentanamide HCl	ISO 17034
Product No.:	V-074-1ML	ISO/IEC 17025
Lot No.:	FC12261805	ISO 13485
Description of CRM:	Valeryl fentanyl HCl in Methanol (Solution)	150 14001
	Nominal concentration is adjusted for HCl content.	150 0001
Retest Date:	February 2022 See Section "Stability Assessment".	130 9001
Storage:	Store unopened in freezer (-10 °C to -25 °C).	<u>^</u>
Shipping:	Ambient. See Section "Stability Assessment".	
Chemical formula:	$C_{24}H_{32}N_2O\bullet HCI$	N I
CAS No.:	117332-91-9	• HCI
Regulatory:	USDEA Schedule I	

Analyte		Certified Concentration \pm associated uncertainty U, $u=k*u$ (k=2)	
Valeryl fenta	nyl	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 3.		
Measurement method:	The certified value characterized star page 3.	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:	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		
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 09, 2021

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 calcuated based on: the actual mass; Mass balance purity factor of the analyte(s); measured mass of the solution; and the density of the pure diluent at 20°C.
- Fill volume is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- Concentration is verified against an independently prepared calibration solution gravimetrically prepared.
- Additional certification information available upon request.

Solution Standard Verification

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

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 (40:60)	Linearity (r) :	1.000
Flow Rate:	1.3 mL/min		
Wavelength:	210 nm		
	Verified Concentration	n (mg/mL) %	RSD - Homogeneity

		Vermed concentration (mg/me)	
Standard Solution	Lot Number	Actual Results	Actual Results
New Lot	FC12261805	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 and salt adjustment are utilized to calculate the weighing adjustment necessary to ensure accuracy of the solution standard concentration.

Material Name:	Valeryl fentanyl HCl	Molecular Wei	ght (base): 364.52		
Material Lot:	FC10031802	Molecular Wei	ght (salt): 400.98		.98
Chemical Formula:	C ₂₄ H ₃₂ N ₂ O•HCl	Salt Adjustme	nt:	1.100	
CAS Number:	117332-91-9			_	
	Material Characte	erization Summary			
Analytical Test		Method	Results		
Primary Chromatographic	Purity by HPLC/UV Analysis	SP10-0102		99.4% ¹	
Secondary Chromatograph	nic Purity by GC/FID Analysis	SP10-0101		99.4% ²	
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 ³	None Detected		
Residual Water Analysis by Karl Fischer Coulometry		AM1346 ³	0.18%		
Inorganic Content by Micro	oash Analysis	SP10-0135	< 0.2%		
				Calculated	Analyzed
Elemental Analysis		Outsourcod	С	71.89%	71.83%
Elemental Analysis		Outsourceu	Н	8.30%	8.11%
			N	6.99%	7.26%
Mass Balance Purity Facto			99.19%		

¹ 0.09% 4-ANPP and 0.03% Butryl fentanyl were detected by HPLC/UV analysis. No Fentanyl detected.

² 0.14% 4-ANPP and 0.03% Butryl fentanyl were detected by GC/FID analysis. No Fentanyl detected.

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	Express C1	8, 2.7 µ	m,
Mohile Phae		nitrile		
	B: 0.1%	Phosphoric	acid in	Water
Gradient:	Time (m	in) % A	% B	
	0.0	10	90	
	8.0	70	30	
	10.0	70	30	
	10.1	10	90	
Flow Rate:	0.7 mL/	min		
Wavelength	1: 210 nm			
_				
Sample Nar	ne: FC1003	1802		
Acquired:	Februar	y 19, 2019		
Peak #	Ret Time	Area %		
1	1.69	0.03		
2	1.75	0.02		
3	3.83	0.01		
4	3.92	0.09		
5	4.70	0.04		
6	4.83	0.01		
/	4.84	0.01		
8	4.93	0.03		
9	5.01	0.01		
10	5.10	0.01		
11	5.24	0.01		
12	5.31	99.33		
13	5.53	0.05		
14	5.61	0.01		
15	5.88	0.01		
16	6.05	0.34		

Peak #4 has been identified as 4-ANPP Peak #8 has been identified as Butyryl fentanyl

GC/FID



Column:	DB-35r 1.0 μm	ns, 30 m x 0.53 mm ID film thickness	,		
Temp Prog	ram: 60°C to hold 27	60°C to 300°C at 20°C/min hold 27 min			
Injector Te Detector Te	emp: Cool-or emp: 325°C	n-Column			
Sample Na Acquired:	me: FC1003 Februar	1802 ry 19, 2019			
Peak #	Ret Time	Area %			
1	8.79	0.01			
2	10.37	0.01			
3	10.79	0.03			
4	12.04	0.01			
5	12.20	0.02			
6	12.27	0.02			
7	12.55	0.14			
8	14.82	0.03			
9	15.69	99.39			
10	15.92	0.02			
11	16.85	0.02			
12	17.09	0.02			
13	19.18	0.28			

Peak #7 has been identified as 4-ANPP Peak #8 has been identified as Butyryl fentanyl

Residual Solvent Analysis by GC/FID Headspace



¹H NMR



JEOL ECS 400

Instrument:





Stability

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

Short Term Stability: A summary of accelerated stability findings for 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 aft		
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 23 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 13, 2019	Initial version.
01	April 24, 2020	Updated Retest Date of May 2020 to February 2021.
0.2	February 09, 2021	Updated Retest Date of February 2021 to February 2022.
02		Updated page reference on first page.



Certified Reference Material - Certificate of Analysis

Valeryl f	entanyl- ¹³ C ₆ , Primary Measurement Standard	Cerilliant Quality
N-Phe	enyl-N-[1-(2-phenylethyl)-4-piperidinyl]-pentanamide- ¹³ C ₆ HCl	ISO 17034
Product No.:	V-0/5-1ML	150/150 17005
Lot No.:	FC12261808	ISO/IEC 17025
Description of CRM:	Valeryl fentanyl- $^{13}C_6$ HCl in Methanol (Solution)	ISO 13485
	Nominal concentration is adjusted for HCl content.	ISO 14001
Retest Date:	November 2021 See Section "Stability Assessment".	ISO 9001
Storage:	Store unopened in freezer (-10 °C to -25 °C).	
Shipping:	Ambient. See Section "Stability Assessment".	•HCI
Chemical formula:	$C_{18}^{13}C_{6}H_{32}N_{2}O \bullet HCI$	[∼] N∕
CAS No.:	NA H ₃ C	
Regulatory:	USDEA Schedule I	

Analyte		Certified Concentration \pm associated uncertainty U, $u=k*u$ (k=2)
Valeryl fentany	∕I- ¹³ C 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 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 quantitati	ive applications
Instructions for handling and correct use:	Concentration is or residual inorganic Users should quar laboratory practic concentration. Eac Nominal concentra- before use. For MS Application sequence.	corrected for chromatographic purity, residual solvents and s. No adjustment required before use. Initiatively 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. ation is adjusted for HCl content. No adjustment required 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.



January 07, 2021

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 calcuated based on: the actual mass; Mass balance purity factor of the analyte(s); measured mass of the solution; and the density of the pure diluent at 20°C.
- Fill volume is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- Concentration is verified against an independently prepared calibration solution gravimetrically prepared.
- Additional certification information available upon request.

Solution Standard Verification

Concentration accuracy and within- and between-bottle homogeneity 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
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 (35:65)	Linearity (r) :	1.000
Flow Rate:	1.2 mL/min		
Wavelength:	210 nm		
	Verified Concentration	. (mg/mL) %	RSD - Homogeneity

		vermed concentration (mg/mL)	70K3D - Holliogeneity
Standard Solution	Lot Number	Actual Results	Actual Results
New Lot	FC12261808	0.997	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 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:	Valeryl fentanyl $^{-13}C_6$ FC10031805 C ₁₈ $^{13}C_6H_{32}N_2O \bullet HCl$ NA	HCI Molecular Mo	Veight (ba Veight (sal ment:	se): lt):	370 406 1.09	.48 .94 98
	Material Cha	aracterization Summary				
Analytical Test		Method		Resu	lts	
Primary Chromatographic Analysis	Purity by HPLC/UV	SP10-0102		99.59	%	
Secondary Chromatograph Analysis	nic Purity by GC/FID	SP10-0101		99.59	%	
Identity by LC/MS Analysi	S	SP10-0107	Consi	stent wit	h St	ructure
Isotopic Purity and Distribution by LC/MS			0.01% $^{13}\mathrm{C}_{0}$ vs $^{13}\mathrm{C}_{6}$			
		CD10 0107	0.01%	0.01% ¹³ C ₀		.08% ¹³ C ₅
Analysis		5910-0107	0.00% $^{13}C_1$ to $^{13}C_3$		97	7.90% ¹³ C ₆
			0.01% ¹³ C ₄			
Identity by ¹ H-NMR Analys	sis	USP <761>, SP10-0116	Consi	stent wit	h St	ructure
Residual Solvent Analysis	by GC/FID Headspace	AM1087 ¹	None Detected			
Residual Water Analysis b Coulometry	y Karl Fischer	AM1346 ¹	Below Quantitation Limit			n Limit
				Calcula	ted	Analyzed
Elemental Analysis		Outcoursed	С	53.13	%	70.69%
Elemental Analysis		Outsourced	н	8.17%	6	8.07%
			Ν	6.88%		7.07%
Inorganic Content by Micr	oash Analysis	SP10-0135	< 0.2%			
Mass Balance Purity Facto	r			99.54	%	

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









	Column: Temp Prog Injector To Detector T	DB-5r 1.5 µr 40°C 200°C hold 1 emp: Cool-c 'emp: 325°C	ns, 30 m x 0.53 mm II n film thickness to 200°C at 40°C/min to 300°C at 5°C/min 6 min on-Column	Э,
	Sample Na Acquired:	i me: FC100 Janua)31805 ry 25, 2019	
	Peak #	Ret Time	Area %	
	1	11.03	0.05	
	2	15.17	0.29	
	3	19.76	0.03	
	4	21.07	99.53	
	5	21.73	0.01	
	6	22.09	0.01	
mn	7	22.40	0.01	
	8	22.57	0.01	
	9	23.04	0.06	

Residual Solvent Analysis by GC/FID Headspace



¹H NMR



V-075-1ML **Revision 03**



Isotopic Purity by LC/MS SIM



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Stability

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

Short Term Stability: A summary of accelerated stability findings for a related product (V-048-0.5ML, Valeryl fentanyl 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 21 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 13, 2019	Initial version.
01	April 01, 2020	Updated Retest Date of April 2020 to January 2021.
		Added Long Term Stability section.
02	May 05, 2020	Corrected Retest Date of January 2021 to February 2021.
03	January 07, 2021	Updated Retest Date of February 2021 to November 2021.