Cerilliant
Analytical Reference Standards
a SIGMA-ALDRICH company

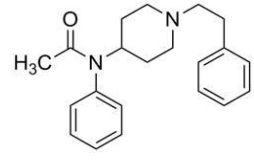
Certified Reference Material - Certificate of Analysis

Acetyl fentanyl, Primary Measurement Standard

N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]-acetamide

Cerilliant Quality
ISO 17034
ISO/IEC 17025
ISO 13485
ISO 14001
ISO 9001

Product No.: A-109-1ML
Lot No.: FC12271801
Description of CRM: Acetyl fentanyl in Methanol (Solution)
Expiration Date: January 2023 See Section "Stability Assessment".
Storage: Store unopened in freezer (-10 °C to -25 °C).
Shipping: Ambient. See Section "Stability Assessment".
Chemical formula: $C_{21}H_{26}N_2O$
CAS No.: 3258-84-2
Regulatory: USDEA schedule I/9821 | Canadian TK # 61-1018



Analyte	Certified Concentration ± 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 µL for quantitative applications

Instructions for handling and correct use: Concentration is corrected for chromatographic purity, residual solvents and residual inorganics. No adjustment required before use.
Users should quantitatively transfer desired volume using established good laboratory practices to spike into matrix or to dilute to the desired concentration. Each ampoule is intended for one-time use.

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

Accreditation: Cerilliant Corp. is accredited by the US accreditation authority ANAB as registered reference material producer AR-1353 in accordance with ISO 17034 and registered testing laboratory AT-1352 according to ISO/IEC 17025.

ANAB ACCREDITED ISO 17034 REFERENCE MATERIAL PRODUCER

Darron Ellsworth, Quality Assurance Manager

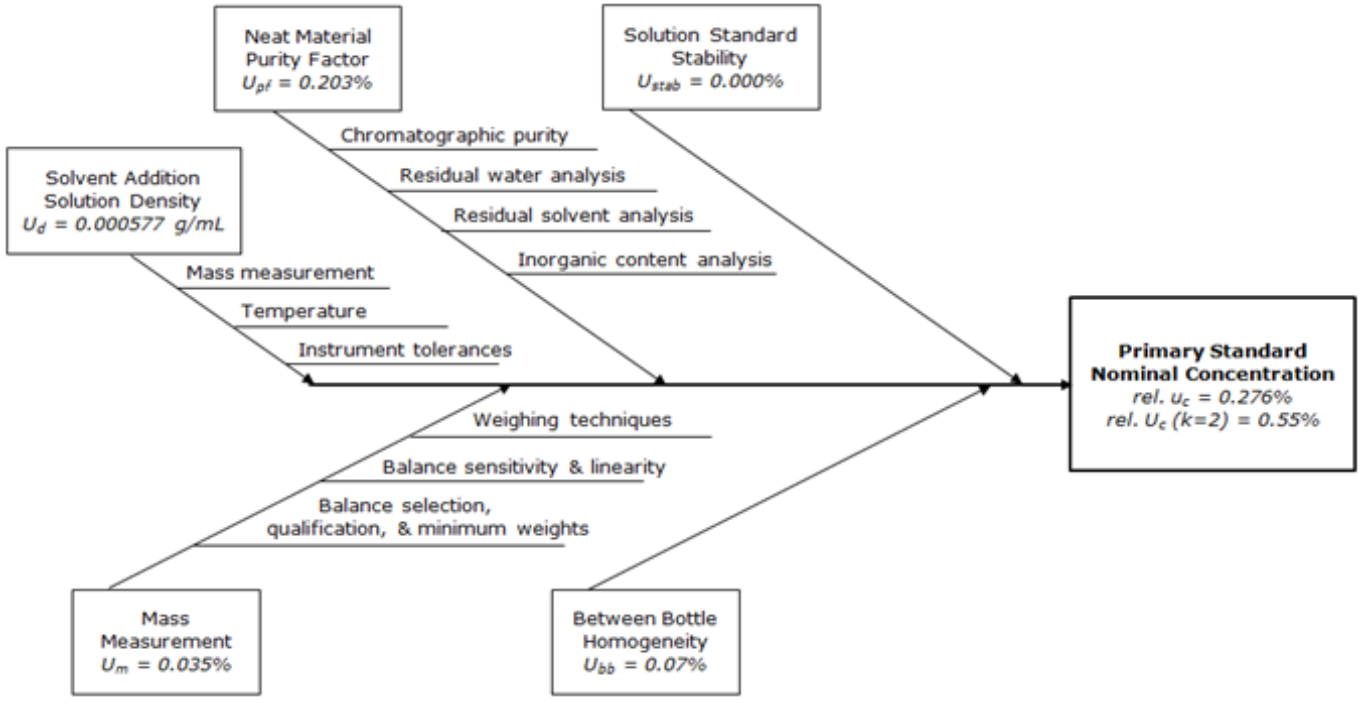
January 17, 2019
Issue Date

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.



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Details on metrological traceability:

- This standard has been gravimetrically prepared using balances that have been fully qualified and calibrated to ISO 17025 requirements. All calibrations utilize NIST traceable weights which are calibrated externally by a qualified ISO 17025 accredited calibration laboratory to NIST standards. Qualification of each balance includes the assignment of a minimum weighing by a qualified and ISO 17025 accredited calibration vendor taking into consideration the balance and installed environmental conditions to ensure compliance with USP tolerances of NMT 0.10% relative error.
- Fill volume to predetermined specifications is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- The density and material Mass Balance Purity Factor of each raw material is traceable to the SI and higher order reference materials through mass measurement and instrument qualification and calibrations.

Details about certification process:

This standard has been prepared and certified under the ISO 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 (mg/mL)	**%RSD - 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.

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Analyte Certification - Mass Balance Purity Factor

Each analyte is thoroughly identified and characterized using an orthogonal approach. A mass balance purity factor is assigned incorporating chromatographic purity and residual impurities. The mass balance purity factor is utilized to calculate the weighing adjustment necessary to ensure accuracy of the solution standard concentration.

Material Name:	Acetyl fentanyl	**Chemical Formula:**	$C_{21}H_{26}N_2O$
Material Lot:	FC10011801	**CAS Number:**	3258-84-2
		Molecular Weight:	322.44

Material Characterization Summary

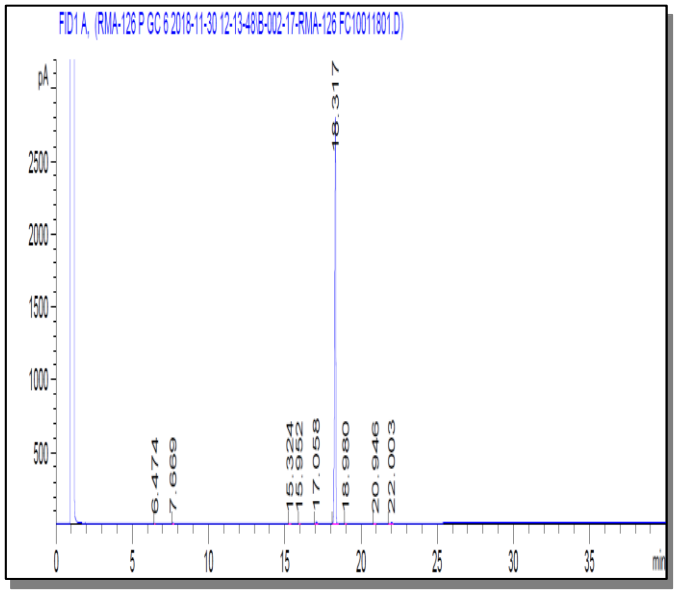
Analytical Test	**Method**	**Results**
Primary Chromatographic Purity by GC/FID Analysis	SP10-0101	99.4% [1]
Secondary Chromatographic Purity by HPLC/UV Analysis	SP10-0102	99.6% [2]
Identity by LC/MS Analysis	SP10-0107	Consistent with Structure
Identity by ^{1}H-NMR Analysis	USP <761>, SP10-0116	Consistent 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 Factor		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



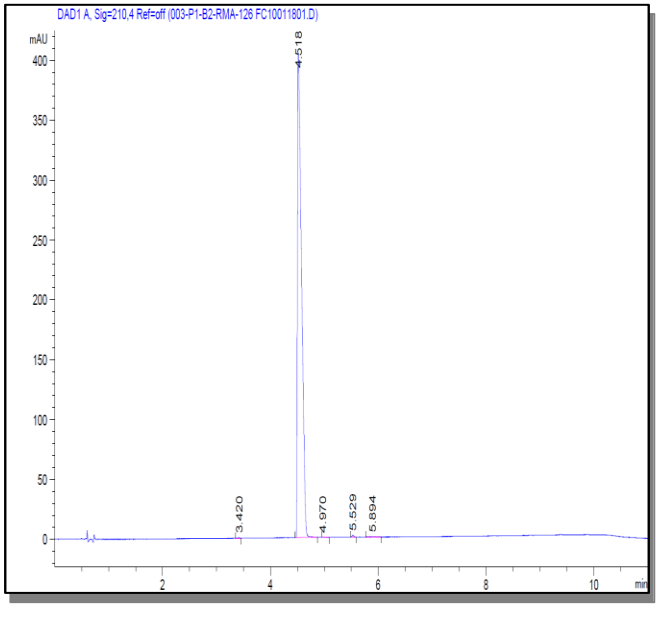
Column: DB-5ms, 30 m x 0.53 mm ID, 1.5 µm film thickness
Temp Program: 40°C to 200°C at 40°C/min
200°C to 300°C at 5°C/min
hold 16 min
Injector Temp: Cool-on-Column
Detector Temp: 325°C

Sample Name: FC10011801
Acquired: November 30, 2018

Peak #	Ret Time	Area %
1	6.47	0.00
2	7.67	0.07
3	15.32	0.02
4	15.95	0.00
5	17.06	0.38
6	18.32	99.36
7	18.98	0.00
8	20.95	0.00
9	22.00	0.16

Peak #3 has been identified as 4-ANPP

HPLC/UV



Column: Ascentis Express Phenyl-Hexyl, 2.7 µm, 3.0 x 100 mm
Mobile Phase: A: Acetonitrile
B: 0.1% Phosphoric 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/min
Wavelength: 210 nm

Sample Name: FC10011801
Acquired: November 29, 2018

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

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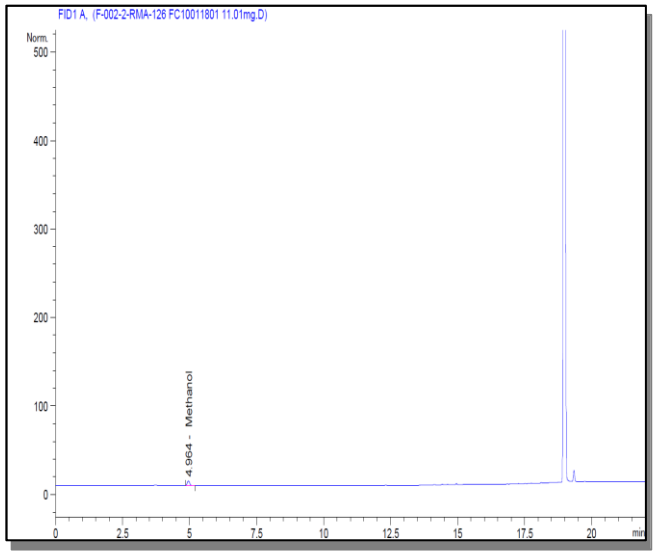
Spectral and Physical Data (cont.)

Residual Solvent Analysis by GC/FID Headspace

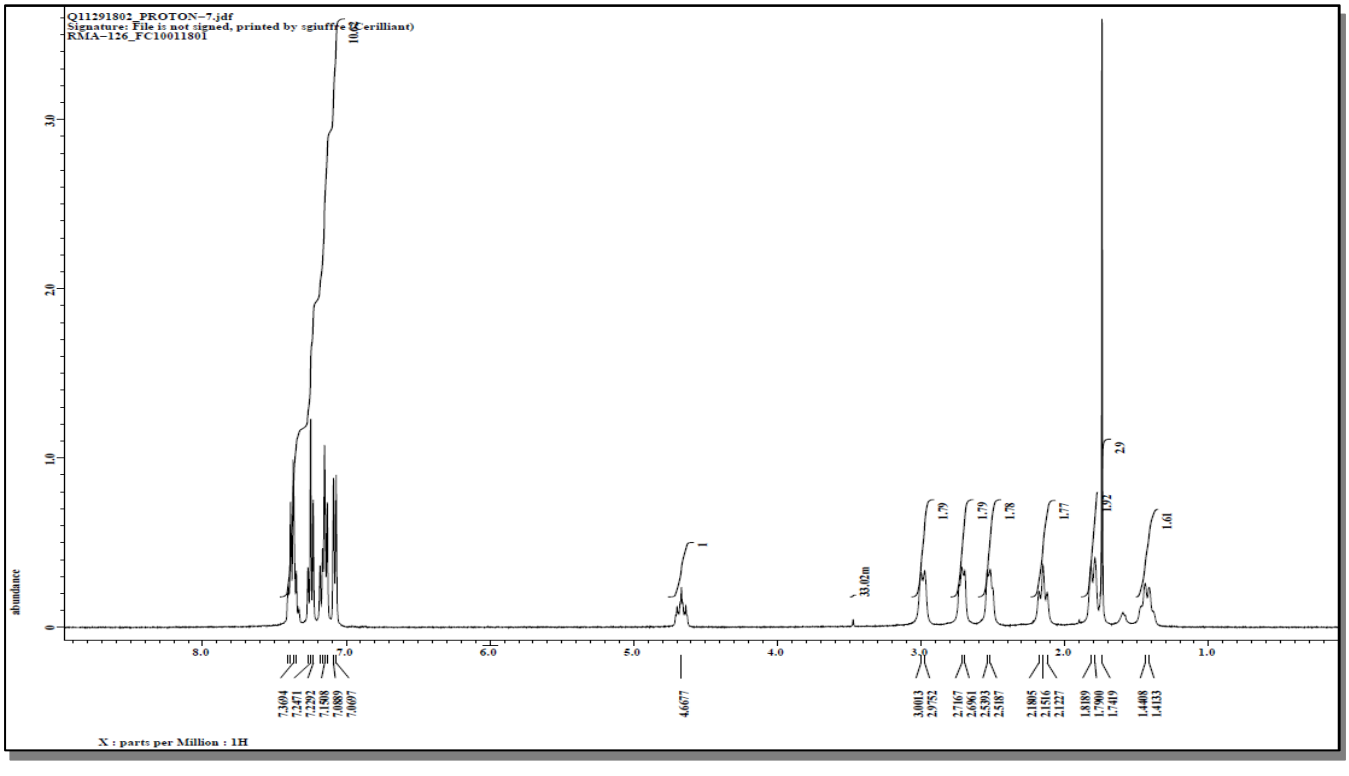


Column:	DB-ALC1 30 m x 0.53 mm, 3 µm film thickness
Temp Program:	40°C hold 12 min to 220°C at 40°C/min hold 5.5 min
Carrier Gas:	Helium
Flow Rate:	2.0 mL/min
Detector Heater Temp:	250°C
Injector:	Headspace Sampler
HS Oven Temp:	60°C
Vial Equilibration:	10 minutes
Sample Name:	FC10011801
Acquired:	November 29, 2018

Peak	Compound	Area	Weight %
1	Methanol	34.27	0.27
2	NMP	NA	NA
Total			**0.27**

^{1}H NMR

Instrument:	JEOL ECS 400
Solvent:	Chloroform-D



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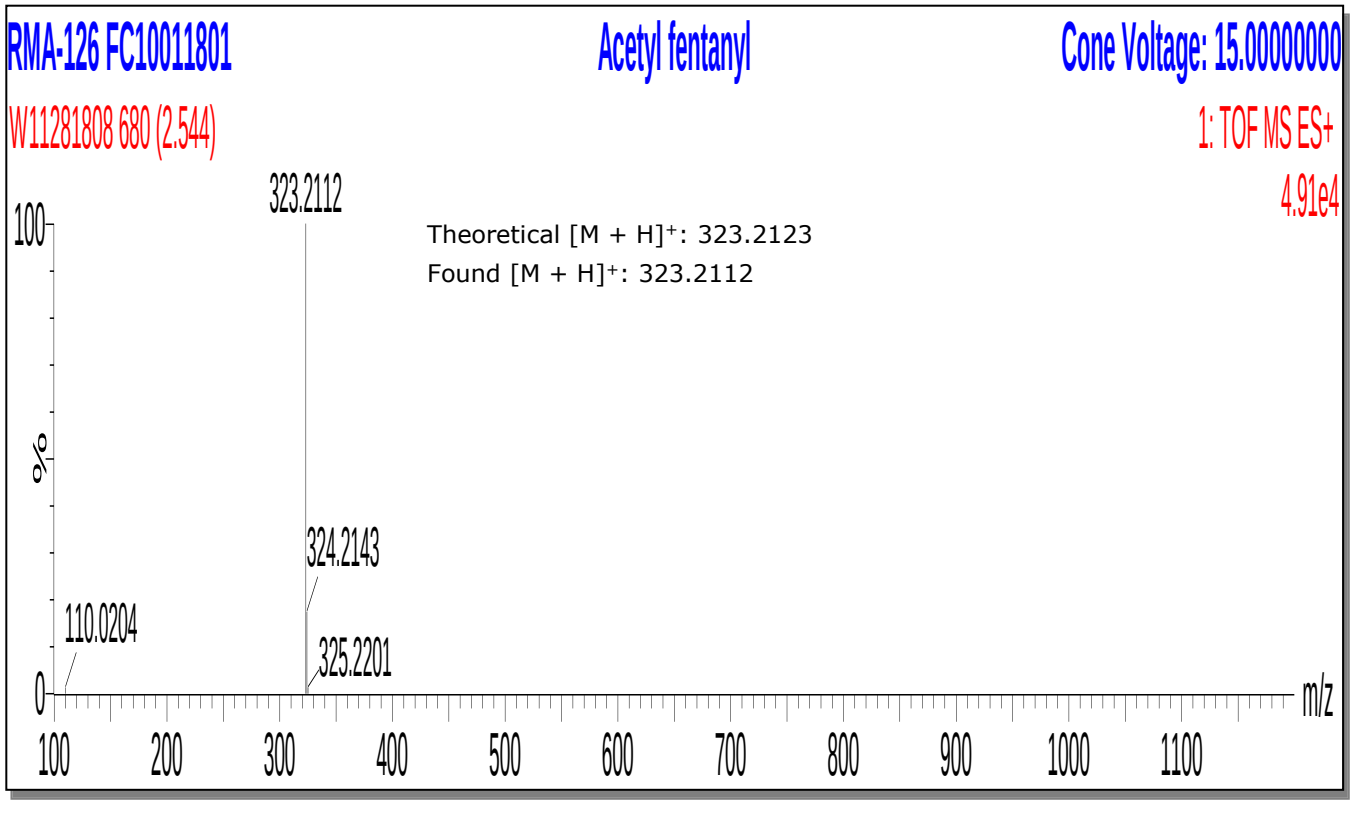
Spectral and Physical Data (cont.)

LC/MS

Column:	Ascentis Express C18, 2.7 µm, 3.0 x 50 mm	**Flow Rate:**	0.4 mL/min
Mobile Phase:	A: 0.1% Formic acid in Water B: Acetonitrile	**Scan Range:**	100-1200 amu
		Ionization:	Electrospray, Positive Ion
		Instrument:	Waters XEVO G2 QTOF
Gradient:		**Acquired:**	November 28, 2018

Time (min)	% A	% B
0.0	90	10
0.5	90	10
4.0	50	50
5.8	50	50
6.0	90	10
8.0	90	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 (A-110, Acetyl fentanyl $^{13}C_6$) is listed below.*

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

Transport/Shipping: *Stability studies support the transport of this product at ambient conditions.*

Long Term Stability: *Long term stability has been assessed for Freezer storage (-10 °C to -25 °C) conditions. Stability of a minimum of 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.

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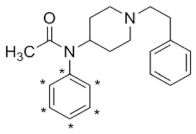
Certified Reference Material - Certificate of Analysis

Acetyl fentanyl-$^{13}C_6$, Primary Measurement Standard

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

Cerilliant Quality
ISO 17034
ISO/IEC 17025
ISO 13485
ISO 14001
ISO 9001

Product No.: A-171-1ML
Lot No.: FC01041901
Description of CRM: Acetyl fentanyl-$^{13}C_6$ in Methanol (Solution)
Retest Date: October 2021 See Section "Stability Assessment".
Storage: Store unopened in freezer (-10 °C to -25 °C).
Shipping: Ambient. See Section "Stability Assessment".
Chemical formula: $C_{15}{}^{13}C_6H_{26}N_2O$
Regulatory: USDEA Schedule I



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

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

Intended use: This Certified Reference Material is suitable for the in vitro identification, calibration, and quantification of the analyte(s) in analytical and R&D applications. Not suitable for human or animal consumption.

Minimum sample size: 1 µL for quantitative applications

Instructions for handling and correct use: Concentration is corrected for chromatographic purity, residual water, residual solvents and residual inorganics. No adjustment required before use.
Users should quantitatively transfer desired volume using established good laboratory practices to spike into matrix or to dilute to the desired concentration. Each ampoule is intended for one-time use.
For MS Applications, we advise laboratories not to mix lots during a single sequence.

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

Accreditation: Cerilliant Corp. is accredited by the US accreditation authority ANAB as registered reference material producer AR-1353 in accordance with ISO 17034 and registered testing laboratory AT-1352 according to ISO/IEC 17025.

Darron Ellsworth, Quality Assurance Manager

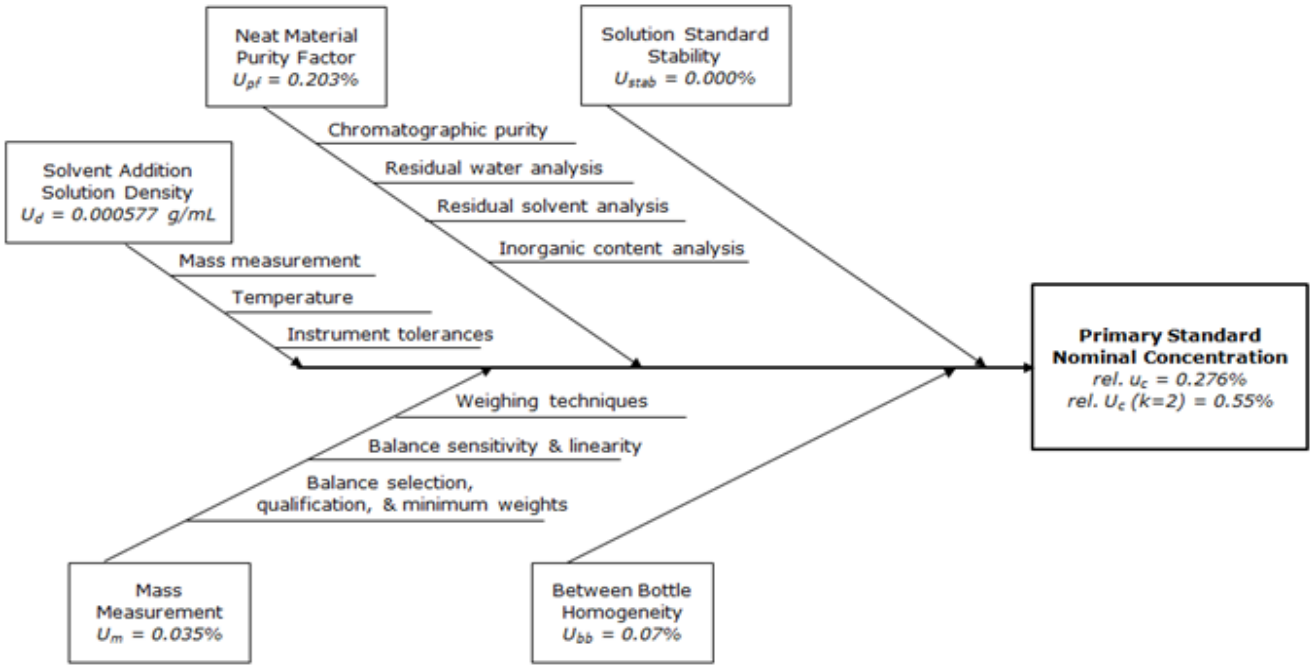
December 01, 2020
Issue Date

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.



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Details on metrological traceability:

- This standard has been gravimetrically prepared using balances that have been fully qualified and calibrated to ISO 17025 requirements. All calibrations utilize NIST traceable weights which are calibrated externally by a qualified ISO 17025 accredited calibration laboratory to NIST standards. Qualification of each balance includes the assignment of a minimum weighing by a qualified and ISO 17025 accredited calibration vendor taking into consideration the balance and installed environmental conditions to ensure compliance with USP tolerances of NMT 0.10% relative error.
- Fill volume to predetermined specifications is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- The density and material Mass Balance Purity Factor of each raw material is traceable to the SI and higher order reference materials through mass measurement and instrument qualification and calibrations.

Details about certification process:

This standard has been prepared and certified under the ISO 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.

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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 50 mm	**Number of Points:**	4
Mobile Phase:	Acetonitrile:0.1% Phosphoric acid in Water (25:75)	**Linearity (r) :**	1.000
Flow Rate:	1.5 mL/min		
Wavelength:	210 nm		

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

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Analyte Certification - Mass Balance Purity Factor

Each analyte is thoroughly identified and characterized using an orthogonal approach. A mass balance purity factor is assigned incorporating chromatographic purity and residual impurities. The mass balance purity factor is utilized to calculate the weighing adjustment necessary to ensure accuracy of the solution standard concentration.

Material Name:	Acetyl fentanyl-$^{13}C_6$	**Chemical Formula:**	$C_{15}{}^{13}C_6H_{26}N_2O$
Material Lot:	FN07251301	**Molecular Weight:**	328.41

Material Characterization Summary

Analytical Test	**Method**	**Results**	
Primary Chromatographic Purity by GC/FID Analysis	SP10-0101	99.7%	
Secondary Chromatographic Purity by HPLPC/UV Analysis	SP10-0102	99.53%	
Identity by LC/MS Analysis	SP10-0107	Consistent with Structure	
Isotopic Purity and Distribution by LC/MS SIM Analysis	SP10-0107	0.00% $^{13}C_0$ vs $^{13}C_6$	
		0.00% $^{13}C_0$	0.04% $^{13}C_4$
		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 Analysis	USP <761>, SP10-0116	Consistent with Structure	
Residual Solvent Analysis by GC/FID Headspace	AM1087 [1]	None Detected	
Residual Water Analysis by Karl Fischer Coulometry	AM1346 [1]	Below Quantitation Limit	
Inorganic Content by Microash Analysis	SP10-0135	< 0.2%	
Mass Balance Purity Factor		99.68%	

[1] Validated analytical method

- The primary chromatographic purity is calculated as the average of two independently performed analyses utilizing two different methods. Acceptance criteria requires the purity values to be within 0.5% of each other.
- The primary purity method was selected to optimize resolution of impurities while minimizing degradation of the analyte. Secondary purity methods with orthogonal detector capabilities from the primary purity method are used as controls to confirm an accurate purity value.
- The primary chromatographic purity value is used to calculate the Mass Balance Purity Factor.
- A secondary chromatographic purity method is utilized as a control.
- Mass Balance Purity Factor = [(100 - wt% residual solvent - wt% residual water - wt% residual inorganics) x Chromatographic Purity/100].
- Mass Balance Purity Factor does not include adjustment for chiral and/or isotopic purity.

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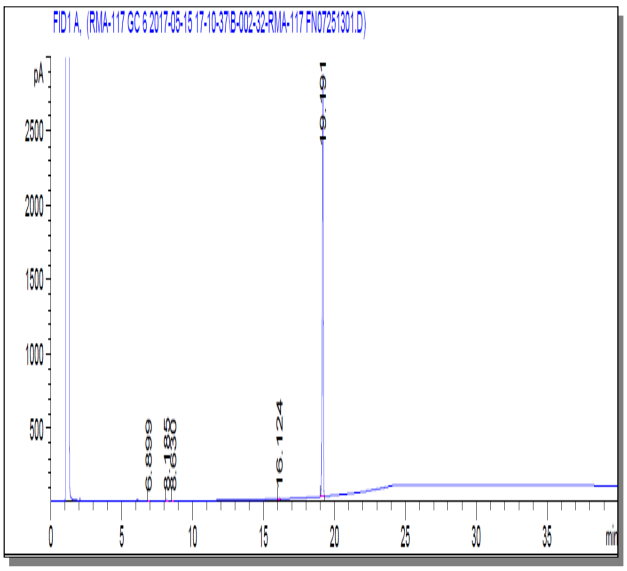
Spectral and Physical Data

GC/FID

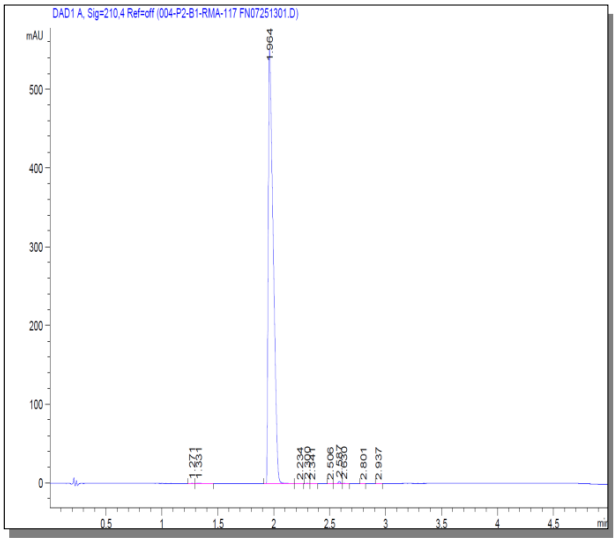


Column: DB-5ms, 30 m x 0.53 mm ID, 1.5 µm film thickness
Temp Program: 40°C to 200°C at 40°C/min
200°C to 300°C at 5°C/min
hold 16 min
Injector Temp: Cool-on-Column
Detector Temp: 325°C

Sample Name: FN07251301
Acquired: May 15, 2017

Peak #	Ret Time	Area %
1	6.90	0.01
2	8.19	0.11
3	8.63	0.02
4	16.12	0.09
5	19.19	99.75

HPLC/UV



Column: Ascentis Express C18, 2.7 µm, 3.0 x 50 mm
Mobile Phase: A: Acetonitrile
B: 0.1% Phosphoric 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/min
Wavelength: 210 nm

Sample Name: FN07251301
Acquired: May 31, 2017

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	2.34	0.02
7	2.51	0.01
8	2.59	0.23
9	2.63	0.03
10	2.80	0.01
11	2.94	0.01

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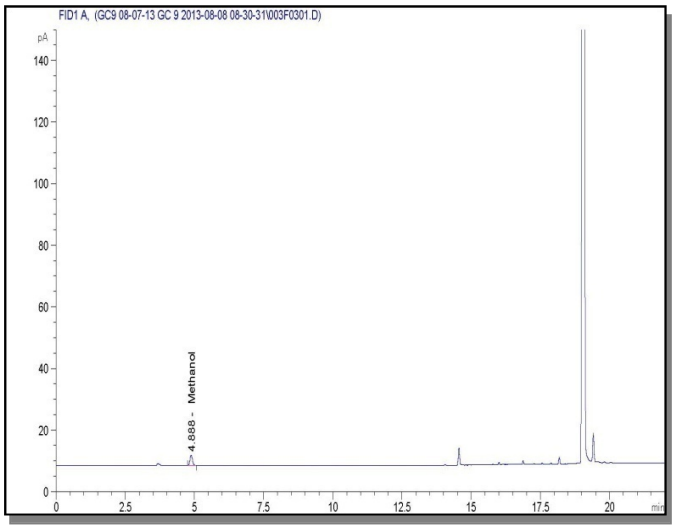
Spectral and Physical Data (cont.)

Residual Solvent Analysis by GC/FID Headspace

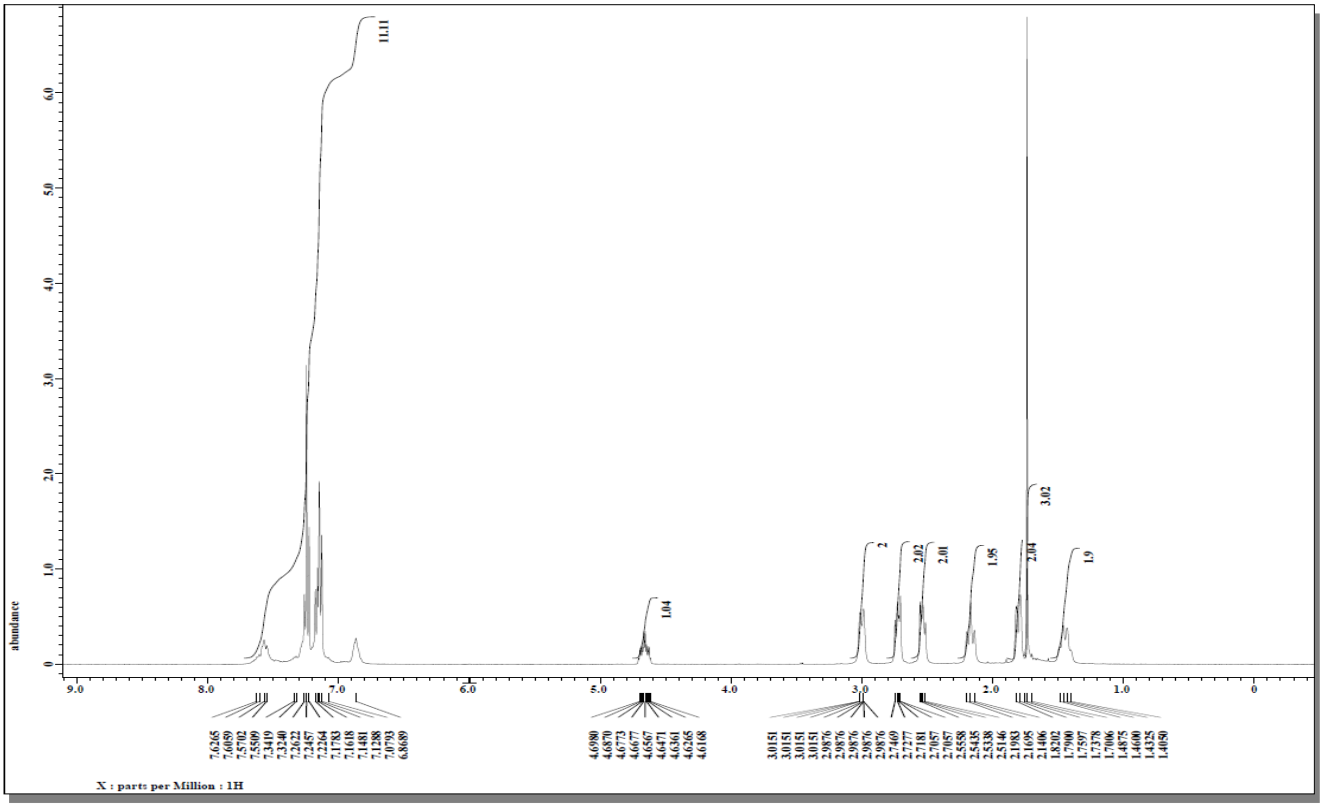


Column:	DB-ALC1 30 m x 0.53 mm, 3 µm film thickness
Temp Program:	40°C hold 12 min to 220°C at 40°C/min hold 5.5 min
Carrier Gas:	Helium
Flow Rate:	2.0 mL/min
Detector Heater Temp:	250°C
Injector:	Headspace Sampler
HS Oven Temp:	60°C
Vial Equilibration:	10 minutes
Sample Name:	FN07251301
Acquired:	August 08, 2013

Peak	Compound	Area	Weight %
1	Methanol	20.73	0.06
2	NMP	NA	NA
Total			**0.06**

^{1}H NMR

Instrument:	JEOL ECS 400
Solvent:	Chloroform-D



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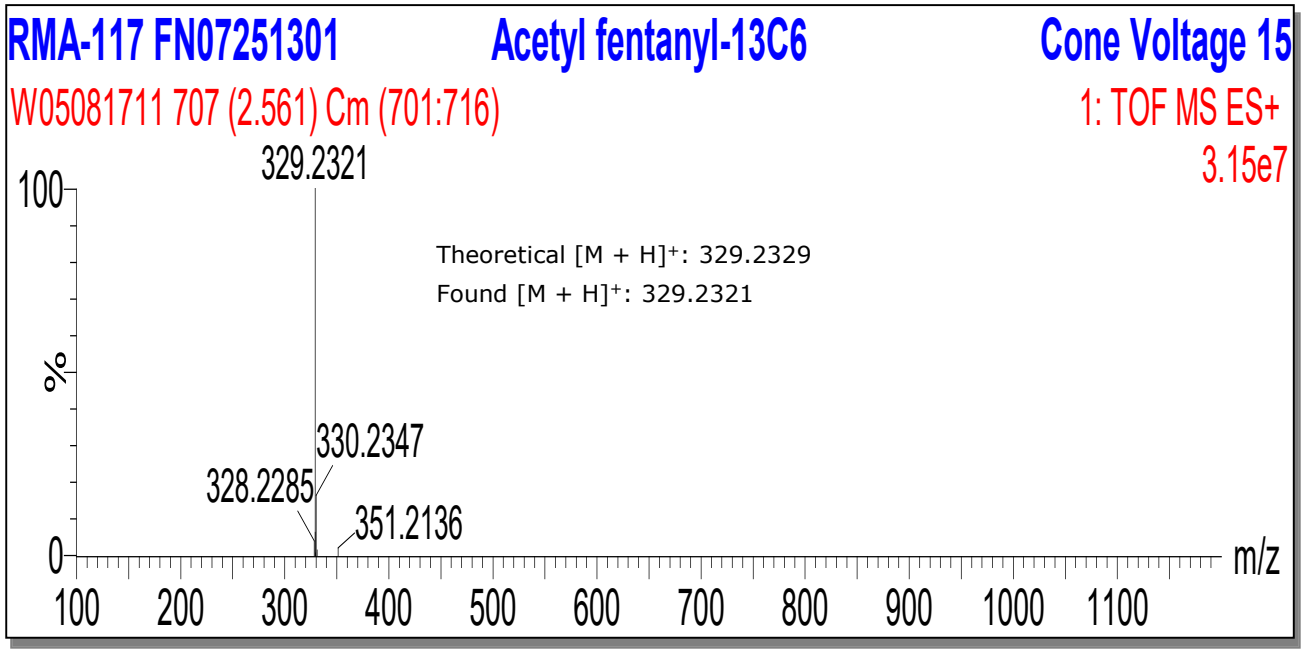
Spectral and Physical Data (cont.)

LC/MS

Column: Ascentis Express C18, 2.7 µm, 3.0 x 50 mm
Mobile Phase: A: 0.1% Formic acid in Water
B: Acetonitrile
Gradient:

Time (min)	% A	% B
0.0	90	10
0.5	90	10
4.0	10	90
5.8	10	90
6.0	90	10
8.0	90	10

Flow Rate: 0.4 mL/min
Scan Range: 100-1200 amu
Ionization: Electrospray, Positive Ion
Instrument: Waters XEVO G2 QTOF
Acquired: May 08, 2017



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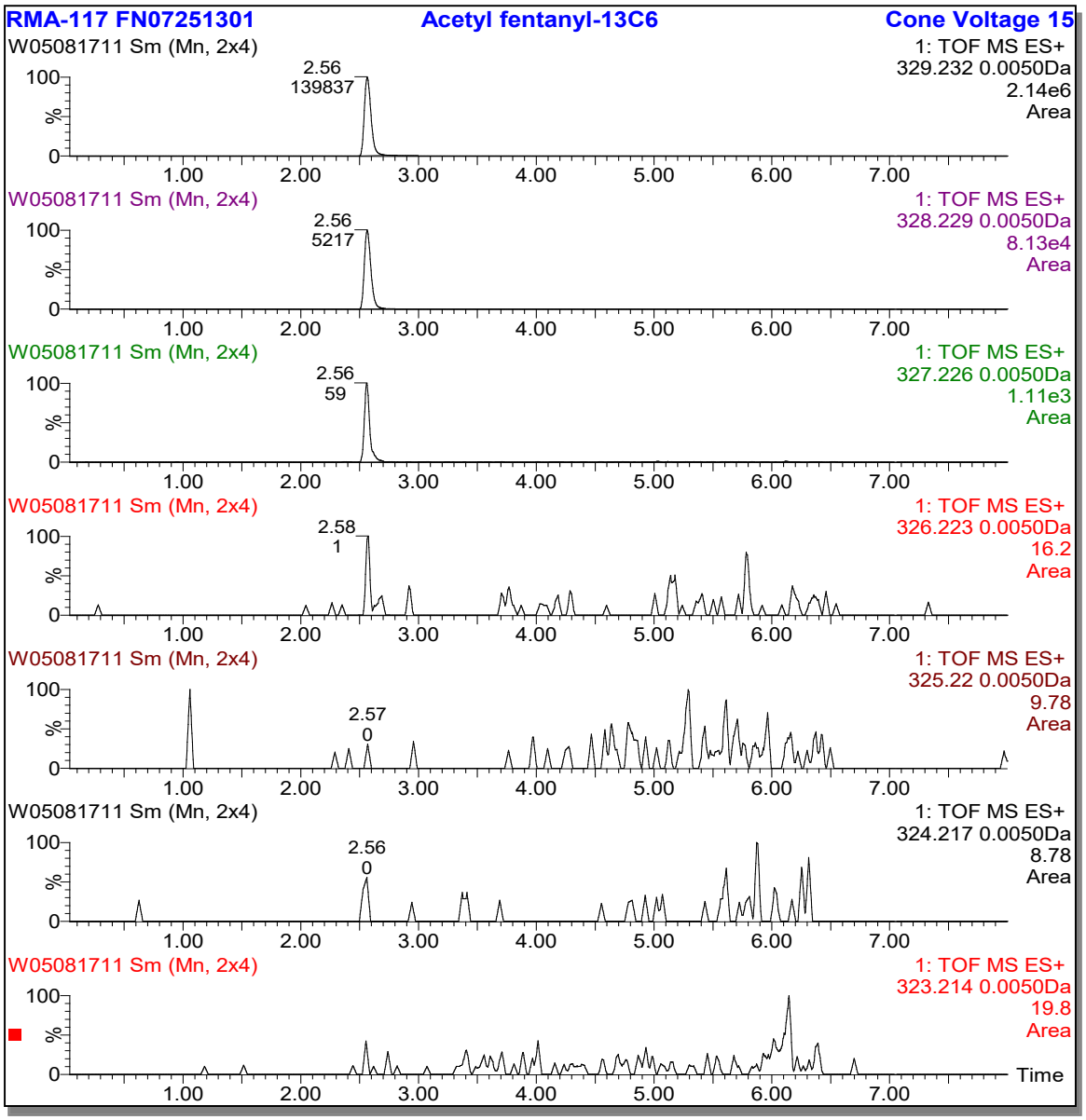
Spectral and Physical Data (cont.)

Isotopic Purity by LC/MS SIM

Column: Ascentis Express C18, 2.7 µm, 3.0 x 50 mm
Mobile Phase: A: 0.1% Formic acid in Water
B: Acetonitrile
Gradient:

Time (min)	% A	% B
0.0	90	10
0.5	90	10
4.0	10	90
5.8	10	90
6.0	90	10
8.0	90	10

Flow Rate: 0.4 mL/min
Scan Range: 323-329 amu
Ionization: Electrospray, Positive Ion
Instrument: Waters XEVO G2 QTOF
Acquired: May 08, 2017



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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 this product is listed below.*

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

Transport/Shipping: *Stability studies support the transport of this product at ambient conditions.*

Long Term Stability: *Long term stability has been assessed for Freezer storage (-10 °C to -25 °C) conditions. Stability of a minimum of 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.

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

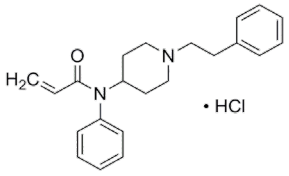
Certified Reference Material - Certificate of Analysis

Acryl fentanyl, Primary Measurement Standard

N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]-2-propenamide HCl;
Acryloyl fentanyl

Cerilliant Quality
ISO 17034
ISO/IEC 17025
ISO 13485
ISO 14001
ISO 9001

Product No.: A-172-1ML
Lot No.: FC01071901
Description of CRM: Acryl fentanyl HCl in Methanol (Solution)
Nominal concentration is adjusted for HCl content.
Retest Date: September 2021 See Section "Stability Assessment".
Storage: Store unopened in freezer (-10 °C to -25 °C).
Shipping: Ambient. See Section "Stability Assessment".
Chemical formula: $C_{22}H_{26}N_2O \bullet HCl$
CAS No.: 79279-03-1
Regulatory: USDEA Schedule I



Analyte	Certified Concentration ± associated uncertainty U, u=k*u (k=2)
Acryl 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 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

September 29, 2020
Issue Date

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

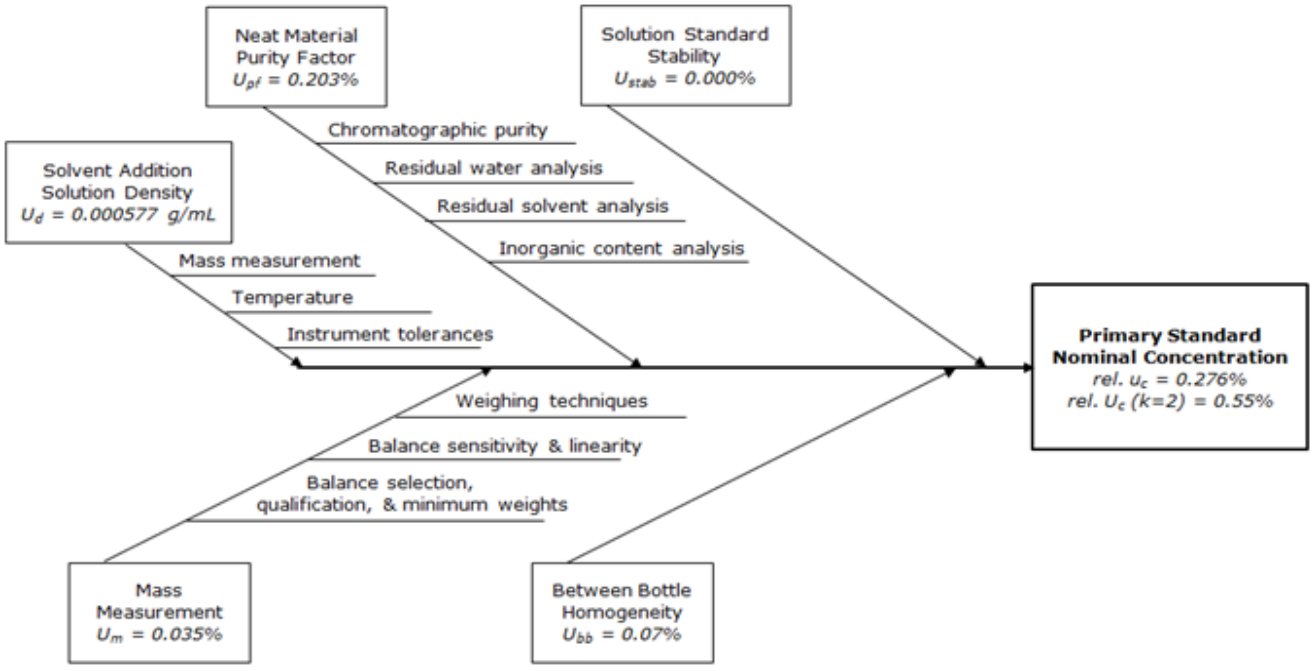
Packaging: 2 mL amber USP Type 1 glass ampoule containing not less than 1 mL of certified solution. Ampoules are overfilled to ensure a minimum of 1 mL volume can be transferred when using a 1mL Class A volumetric pipette.

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.



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Details on metrological traceability:

- This standard has been gravimetrically prepared using balances that have been fully qualified and calibrated to ISO 17025 requirements. All calibrations utilize NIST traceable weights which are calibrated externally by a qualified ISO 17025 accredited calibration laboratory to NIST standards. Qualification of each balance includes the assignment of a minimum weighing by a qualified and ISO 17025 accredited calibration vendor taking into consideration the balance and installed environmental conditions to ensure compliance with USP tolerances of NMT 0.10% relative error.
- Fill volume to predetermined specifications is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- The density and material Mass Balance Purity Factor of each raw material is traceable to the SI and higher order reference materials through mass measurement and instrument qualification and calibrations.

Details about certification process:

This standard has been prepared and certified under the ISO 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.

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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 Concentration (mg/mL)	**%RSD - Homogeneity**
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.

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Analyte Certification - Mass Balance Purity Factor

Each analyte is thoroughly identified and characterized using an orthogonal approach. A mass balance purity factor is assigned incorporating chromatographic purity and residual impurities. The mass balance purity factor 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 Weight (base):**	334.45
Material Lot:	FC10011803	**Molecular Weight (salt):**	370.92
Chemical Formula:	$C_{22}H_{26}N_2O \bullet HCl$	**Salt Adjustment:**	1.109
CAS Number:	79279-03-1		

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	99.5%		
Identity by LC/MS Analysis	SP10-0107	Consistent with Structure		
Identity by ^{1}H-NMR Analysis	USP <761>, SP10-0116	Consistent with Structure		
Residual Solvent Analysis by GC/FID Headspace	AM1087 [2]	0.13%		
Residual Water Analysis by Karl Fischer Coulometry	AM1346 [2]	Not Detected		
Inorganic Content by Microash Analysis	SP10-0135	< 0.2%		
Elemental Analysis	Outsourced		Calculated	Analyzed
		C	71.24%	71.31%
		H	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.

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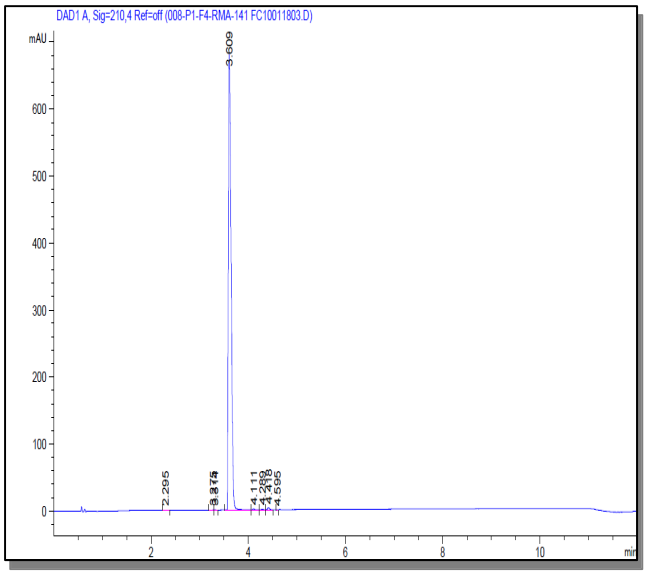
Spectral and Physical Data

HPLC/UV



Column: Ascentis Express C18, 2.7 µm 3.0 x 100 mm

Mobile Phase: A: Acetonitrile
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/min

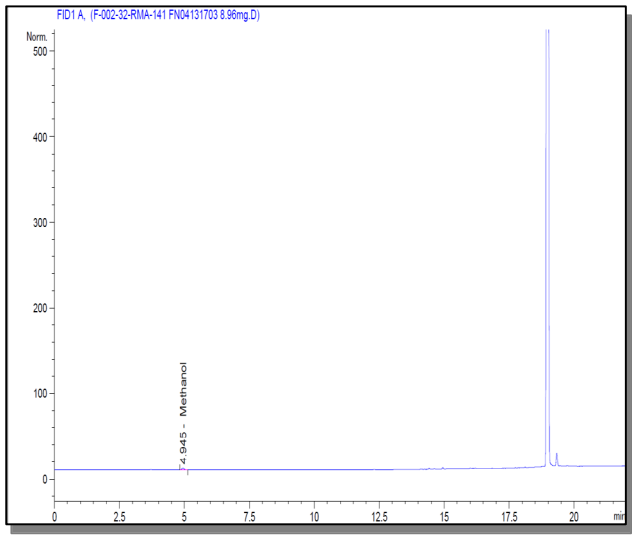
Wavelength: 210 nm

Sample Name: FC10011803

Acquired: December 04, 2018

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
8	4.60	0.01

Residual Solvent Analysis by GC/FID Headspace



Column: DB-ALC1 30 m x 0.53 mm, 3 µm film thickness

Temp Program: 40°C hold 12 min to 220°C at 40°C/min hold 5.5 min

Carrier Gas: Helium

Flow Rate: 2.0 mL/min

Detector Heater Temp: 250°C

Injector: Headspace Sampler

HS Oven Temp: 60°C

Vial Equilibration: 10 minutes

Sample Name: FC10011803

Acquired: December 06, 2018

Peak	Compound	Area	Weight %
1	Methanol	13.20	0.13
2	NMP	NA	NA
Total			**0.13**

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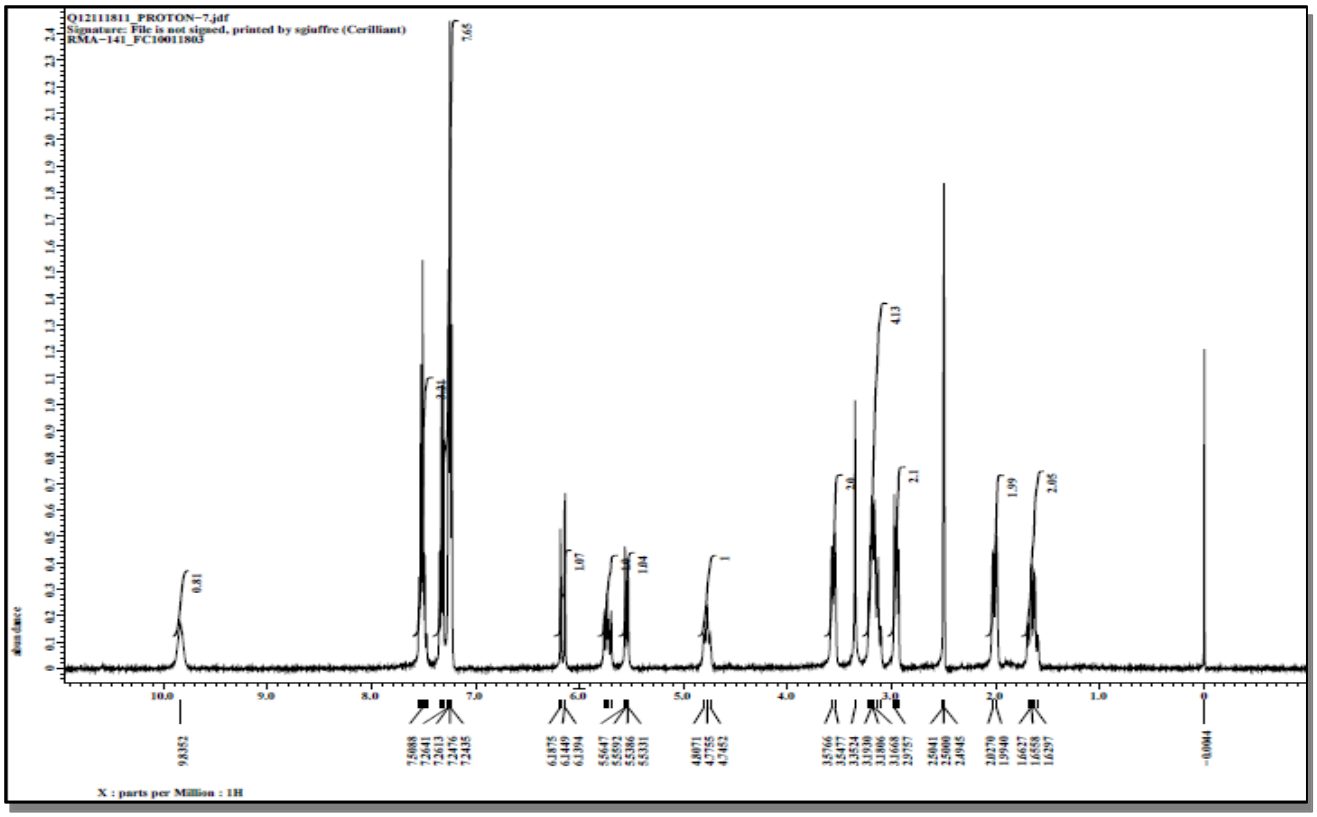
Spectral and Physical Data (cont.)

^{1}H NMR

Instrument: JEOL ECS 400
Solvent: DMSO-D_6



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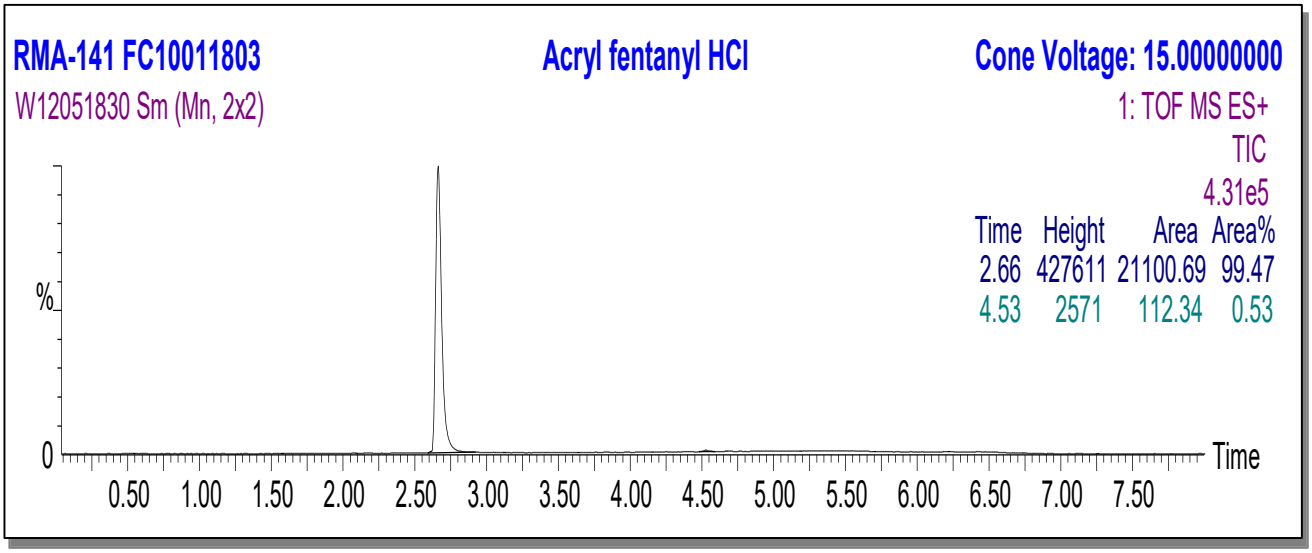
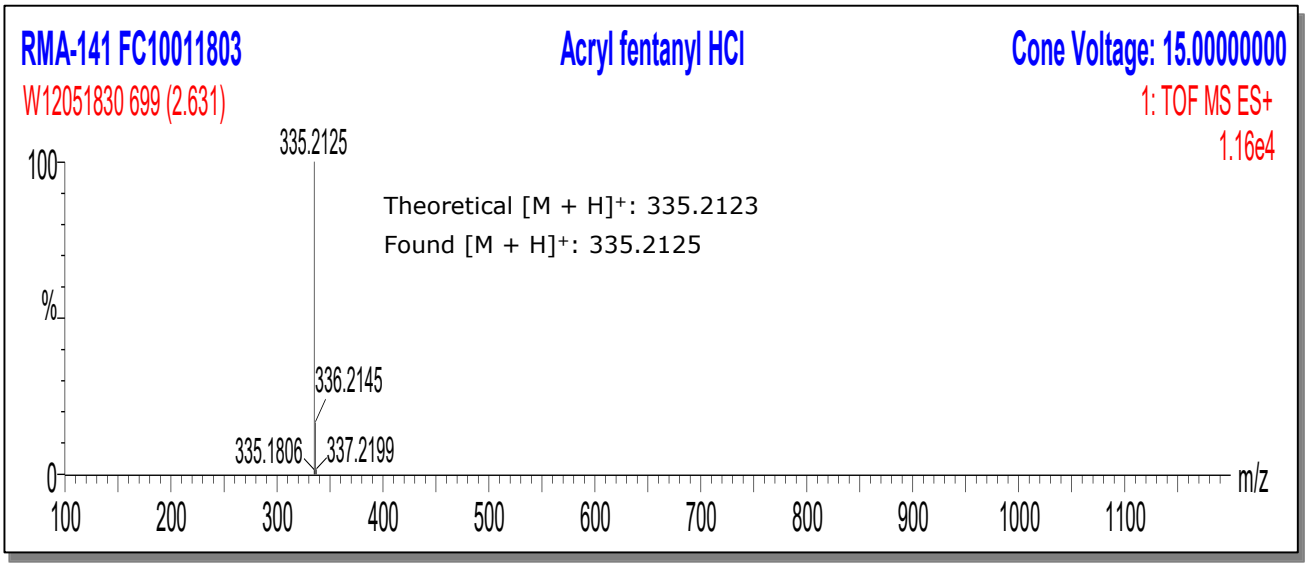
Spectral and Physical Data (cont.)

LC/MS

Column:	Ascentis Express C18, 2.7 µm, 3.0 x 50 mm	**Flow Rate:**	0.4 mL/min
Mobile Phase:	A: 0.1% Formic acid in Water B: Acetonitrile	**Scan Range:**	100-1200 amu
		Ionization:	Electrospray, Positive Ion
		Instrument:	Waters XEVO G2 QTOF
Gradient:		**Acquired:**	December 05, 2018

Time (min)	% A	% B
0.0	90	10
0.5	90	10
4.0	50	50
5.8	50	50
6.0	90	10
8.0	90	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 this product is listed below.*

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

Transport/Shipping: *Stability studies support the transport of this product at ambient conditions.*

Long Term Stability: *Long term stability has been assessed for Freezer storage (-10 °C to -25 °C) conditions. Stability of a minimum of 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 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.

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

Certified Reference Material - Certificate of Analysis

Acryl fentanyl-$^{13}C_6$, Primary Measurement Standard

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

Cerilliant Quality
ISO 17034
ISO/IEC 17025
ISO 13485
ISO 14001
ISO 9001

Product No.: A-173-1ML

Lot No.: FC01081901

Description of CRM: Acryl fentanyl-$^{13}C_6$ HCl in Methanol (Solution)
Nominal concentration is adjusted for HCl content.

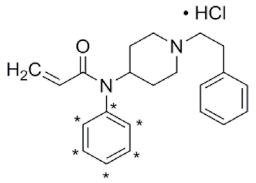
Retest Date: September 2021 See Section "Stability Assessment".

Storage: Store unopened in freezer (-10 °C to -25 °C).

Shipping: Ambient. See Section "Stability Assessment".

Chemical formula: $C_{16}{}^{13}C_6H_{26}N_2O \bullet HCl$

Regulatory: USDEA Schedule I



Analyte	Certified Concentration ± associated uncertainty U, u=k*u (k=2)
Acryl 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.

Darron Ellsworth, Quality Assurance Manager

September 29, 2020
Issue Date

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

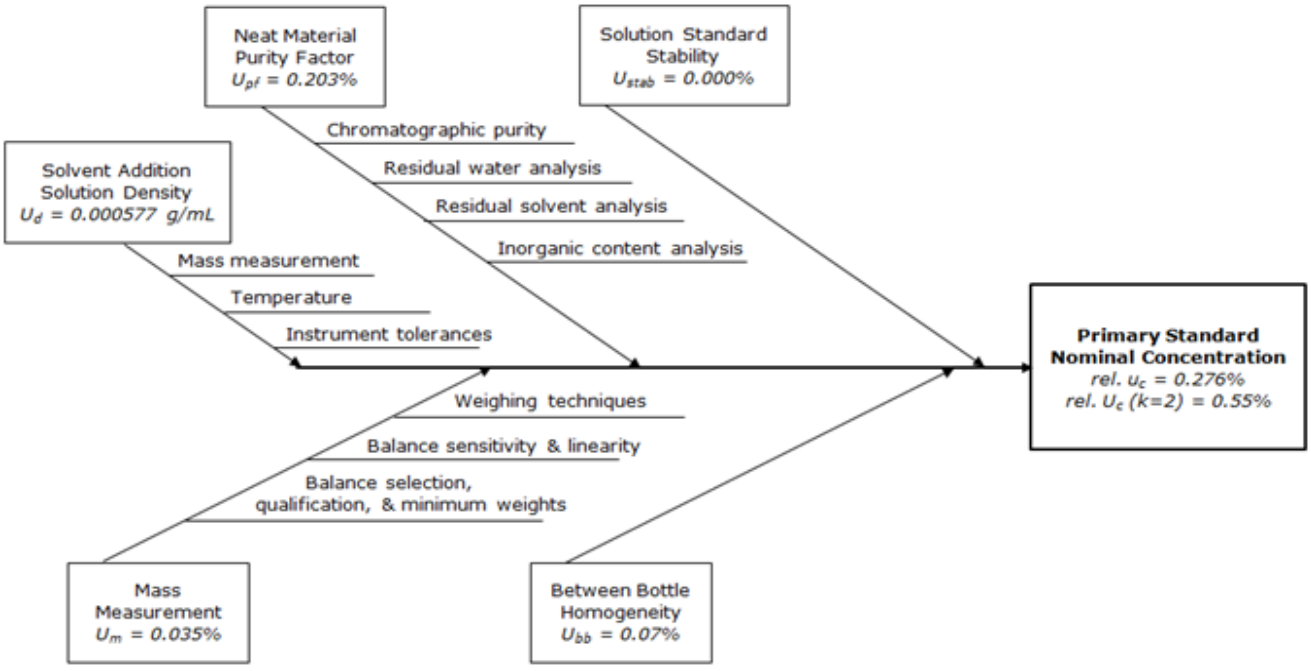
Packaging: 2 mL amber USP Type 1 glass ampoule containing not less than 1 mL of certified solution. Ampoules are overfilled to ensure a minimum of 1 mL volume can be transferred when using a 1mL Class A volumetric pipette.

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.



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Details on metrological traceability:

- This standard has been gravimetrically prepared using balances that have been fully qualified and calibrated to ISO 17025 requirements. All calibrations utilize NIST traceable weights which are calibrated externally by a qualified ISO 17025 accredited calibration laboratory to NIST standards. Qualification of each balance includes the assignment of a minimum weighing by a qualified and ISO 17025 accredited calibration vendor taking into consideration the balance and installed environmental conditions to ensure compliance with USP tolerances of NMT 0.10% relative error.
- Fill volume to predetermined specifications is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- The density and material Mass Balance Purity Factor of each raw material is traceable to the SI and higher order reference materials through mass measurement and instrument qualification and calibrations.

Details about certification process:

This standard has been prepared and certified under the ISO 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.

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

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 Concentration (mg/mL)	**%RSD - 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.

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Analyte Certification - Mass Balance Purity Factor

Each analyte is thoroughly identified and characterized using an orthogonal approach. A mass balance purity factor is assigned incorporating chromatographic purity and residual impurities. The mass balance purity factor and salt adjustment are utilized to calculate the weighing adjustment necessary to ensure accuracy of the solution standard concentration.

Material Name:	Acryl fentanyl-$^{13}C_6$ HCl	**Molecular Weight (base):**	340.41
Material Lot:	FC10101803	**Molecular Weight (salt):**	376.87
Chemical Formula:	$C_{16}{}^{13}C_6H_{26}N_2O \bullet HCl$	**Salt Adjustment:**	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	
Isotopic Purity and Distribution by LC/MS SIM Analysis	SP10-0107	0.01% $^{13}C_0$ vs $^{13}C_6$	
		0.01% $^{13}C_0$	0.02% $^{13}C_4$
		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.

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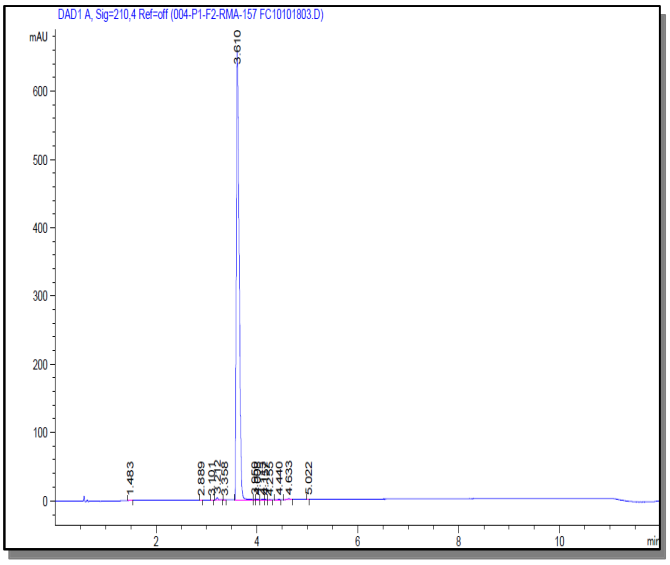
Spectral and Physical Data

HPLC/UV



Column: Ascentis Express C18, 2.7 µm, 3.0 x 100 mm

Mobile Phase: A: Acetonitrile
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/min

Wavelength: 210 nm

Sample Name: FC10101803

Acquired: December 10, 2018

Peak #	Ret Time	Area %
1	1.48	0.04
2	2.89	0.01
3	3.10	0.00
4	3.21	0.32
5	3.36	0.01
6	3.61	99.30
7	3.95	0.02
8	4.01	0.05
9	4.11	0.06
10	4.16	0.02
11	4.26	0.01
12	4.44	0.02
13	4.63	0.13
14	5.02	0.00

Peak #4 has been identified as 4-ANPP

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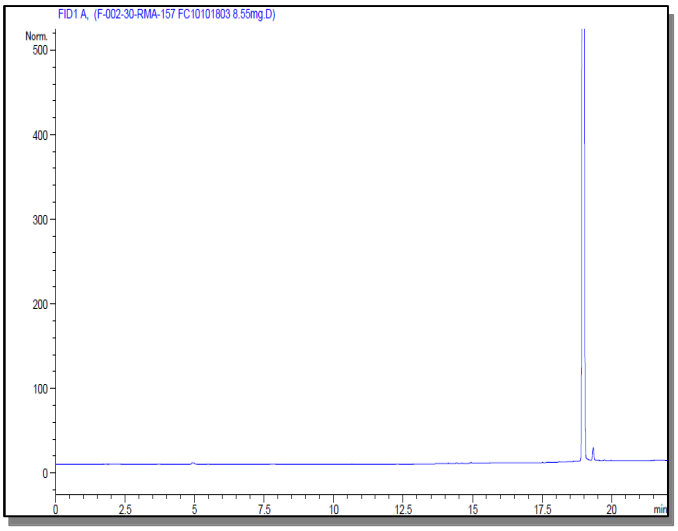
Spectral and Physical Data (cont.)

Residual Solvent Analysis by GC/FID Headspace



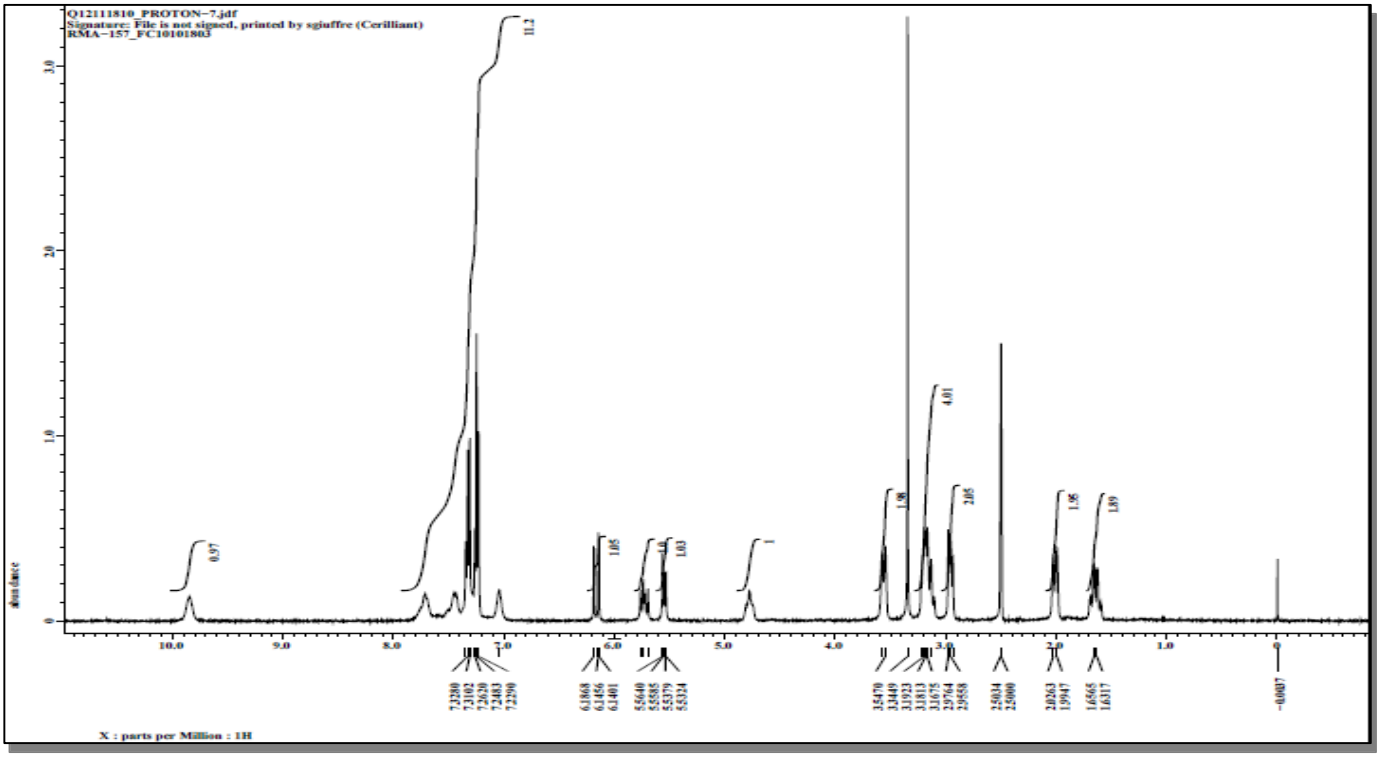
Column:	DB-ALC1 30 m x 0.53 mm, 3 µm film thickness
Temp Program:	40°C hold 12 min to 220°C at 40°C/min hold 5.5 min
Carrier Gas:	Helium
Flow Rate:	2.0 mL/min
Detector Heater Temp:	250°C
Injector:	Headspace Sampler
HS Oven Temp:	60°C
Vial Equilibration:	10 minutes
Sample Name:	FC10101803
Acquired:	December 06, 2018

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

ND - None Detected

^{1}H NMR

Instrument: JEOL ECS 400
Solvent: DMSO-D_6



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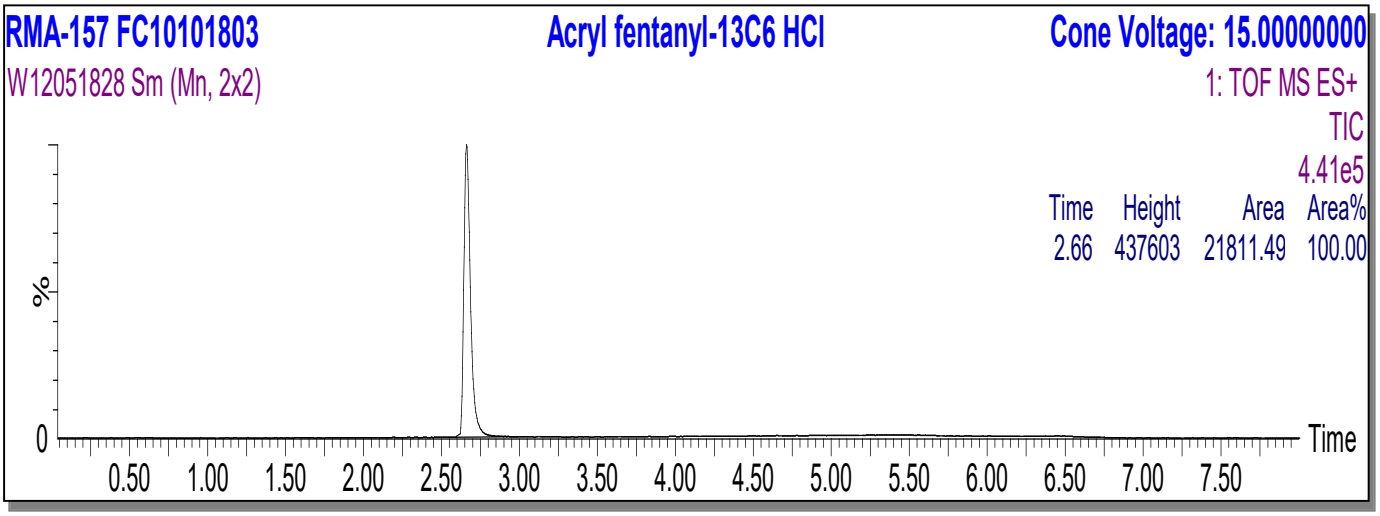
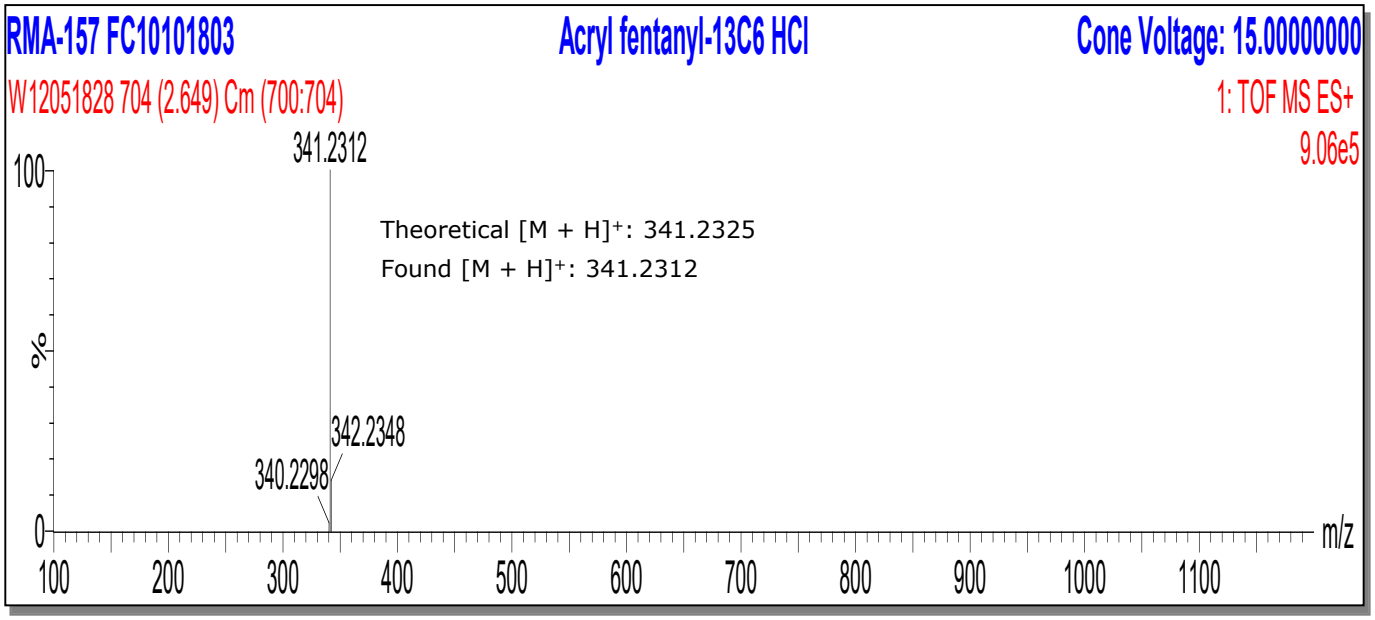
Spectral and Physical Data (cont.)

LC/MS

Column:	Ascentis Express C18, 2.7 µm, 3.0 x 50 mm	**Flow Rate:**	0.4 mL/min
Mobile Phase:	A: 0.1% Formic acid in Water B: Acetonitrile	**Scan Range:**	100-1200 amu
		Ionization:	Electrospray, Positive Ion
		Instrument:	Waters XEVO G2 QTOF
Gradient:		**Acquired:**	December 05, 2018

Time (min)	% A	% B
0.0	90	10
0.5	90	10
4.0	50	50
5.8	50	50
6.0	90	10
8.0	90	10





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Spectral and Physical Data (cont.)

Isotopic Purity by LC/MS SIM

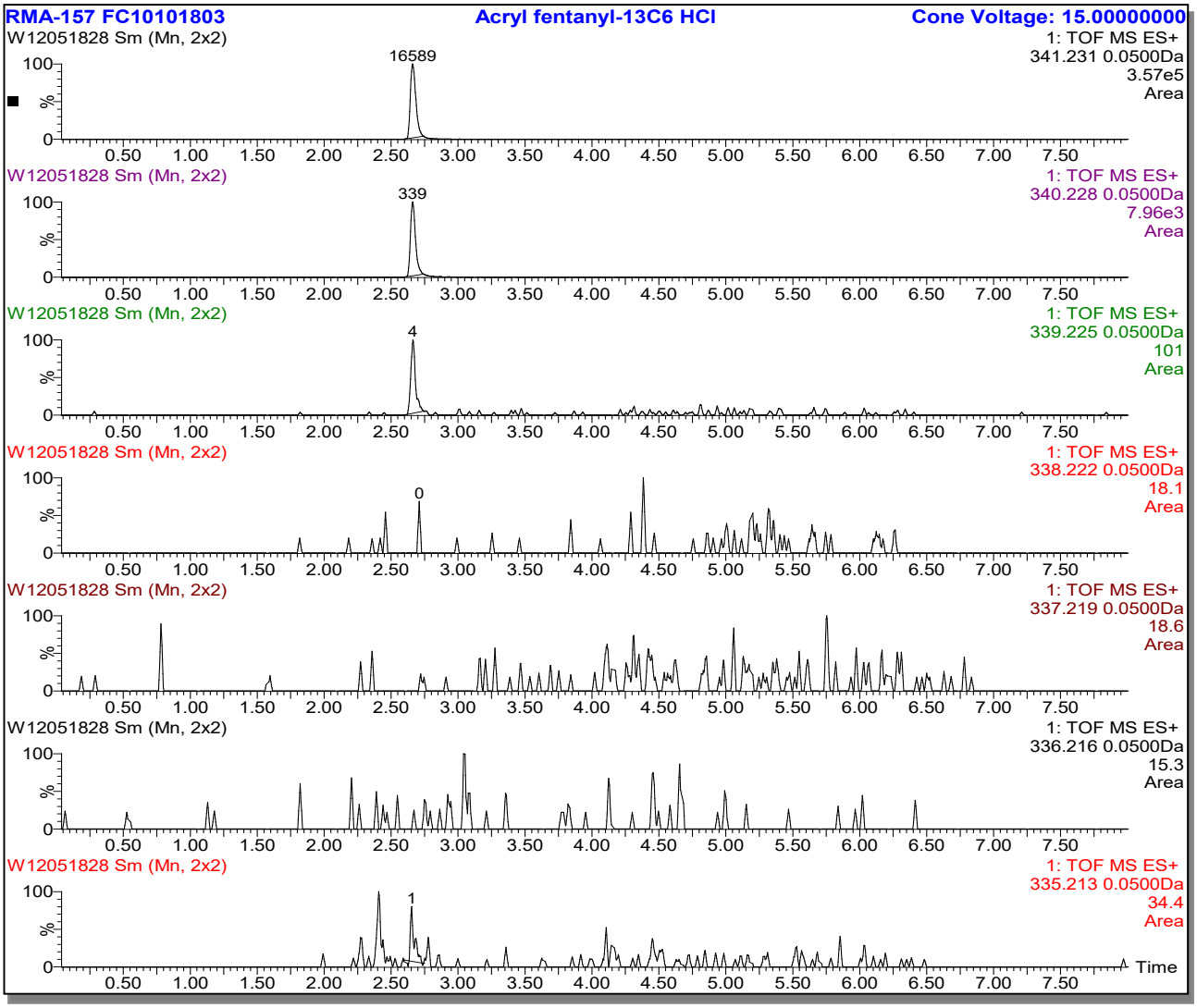
Column: Ascentis Express C18, 2.7 µm, 3.0 x 50 mm

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

Gradient:

Time (min)	% A	% B
0.0	90	10
0.5	90	10
4.0	50	50
5.8	50	50
6.0	90	10
8.0	90	10

Flow Rate: 0.4 mL/min
Scan Range: 335-341 amu
Ionization: Electrospray, Positive Ion
Instrument: Waters XEVO G2 QTOF
Acquired: December 05, 2018



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Stability

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

Short Term Stability: *A summary of accelerated stability findings for a related product (A-140-0.5ML, Acryl fentanyl HCl) is listed below.*

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

Transport/Shipping: *Stability studies support the transport of this product at ambient conditions.*

Long Term Stability: *Long term stability has been assessed for Freezer storage (-10 °C to -25 °C) conditions. Stability of a minimum of 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.

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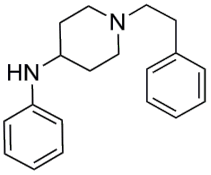
Certified Reference Material - Certificate of Analysis

4-ANPP, Primary Measurement Standard

N-Phenyl-1-(2-phenethyl)-4-piperidinamine

Cerilliant Quality
ISO 17034
ISO/IEC 17025
ISO 13485
ISO 14001
ISO 9001

Product No.: A-174-1ML
Lot No.: FC01141902
Description of CRM: 4-ANPP in Methanol (Solution)
Retest Date: December 2021 See Section "Stability Assessment".
Storage: Store unopened in freezer (-10 °C to -25 °C).
Shipping: Ambient. See Section "Stability Assessment".
Chemical formula: $C_{19}H_{24}N_2$
CAS No.: 21409-26-7
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 µL for quantitative applications

Instructions for handling and correct use: Concentration is corrected for chromatographic purity, residual water, residual solvents and residual inorganics. No adjustment required before use.
Users should quantitatively transfer desired volume using established good laboratory practices to spike into matrix or to dilute to the desired concentration. Each ampoule is intended for one-time use.

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

Accreditation: Cerilliant Corp. is accredited by the US accreditation authority ANAB as registered reference material producer AR-1353 in accordance with ISO 17034 and registered testing laboratory AT-1352 according to ISO/IEC 17025.

ANAB ACCREDITED ISO 17034 REFERENCE MATERIAL PRODUCER

Darron Ellsworth, Quality Assurance Manager

December 29, 2020
Issue Date

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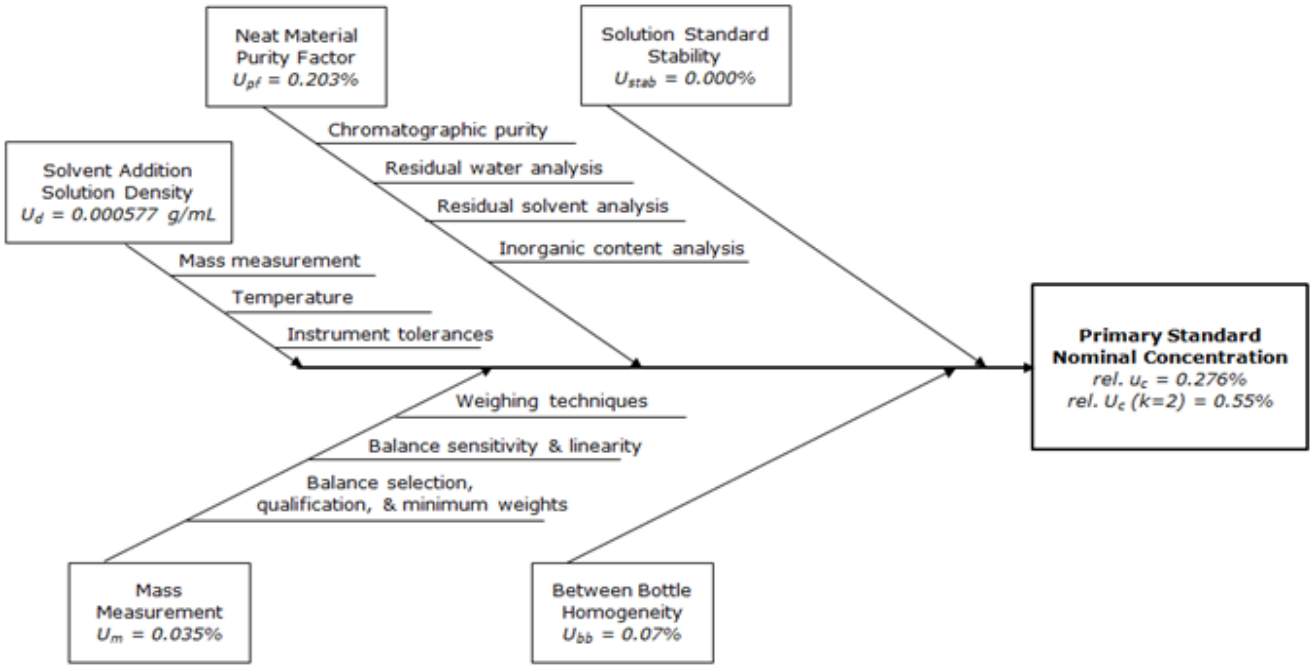
Packaging:	2 mL amber USP Type 1 glass ampoule containing not less than 1 mL of certified solution. Ampoules are overfilled to ensure a minimum of 1 mL volume can be transferred when using a 1mL Class A volumetric pipette.
Details on starting materials:	Each raw material utilized has been identified 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.



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Details on metrological traceability:

- This standard has been gravimetrically prepared using balances that have been fully qualified and calibrated to ISO 17025 requirements. All calibrations utilize NIST traceable weights which are calibrated externally by a qualified ISO 17025 accredited calibration laboratory to NIST standards. Qualification of each balance includes the assignment of a minimum weighing by a qualified and ISO 17025 accredited calibration vendor taking into consideration the balance and installed environmental conditions to ensure compliance with USP tolerances of NMT 0.10% relative error.
- Fill volume to predetermined specifications is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- The density and material Mass Balance Purity Factor of each raw material is traceable to the SI and higher order reference materials through mass measurement and instrument qualification and calibrations.

Details about certification process:

This standard has been prepared and certified under the ISO 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.

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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		

		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.

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Analyte Certification - Mass Balance Purity Factor

Each analyte is thoroughly identified and characterized using an orthogonal approach. A mass balance purity factor is assigned incorporating chromatographic purity and residual impurities. The mass balance purity factor is utilized to calculate the weighing adjustment necessary to ensure accuracy of the solution standard concentration.

Material Name:	4-ANPP	**Chemical Formula:**	$C_{19}H_{24}N_2$
Material Lot:	FC10041801	**CAS Number:**	21409-26-7
		Molecular Weight:	280.41

Material Characterization Summary

Analytical Test	Method	Results
Primary Chromatographic 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 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		99.69%

[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.

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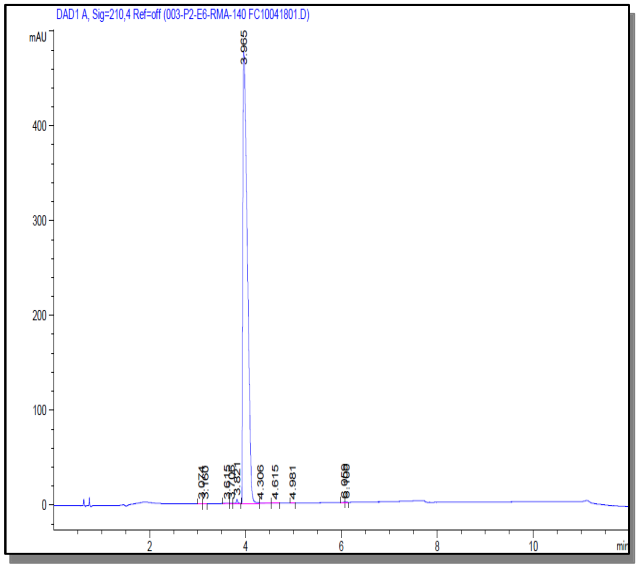
Spectral and Physical Data

HPLC/UV



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

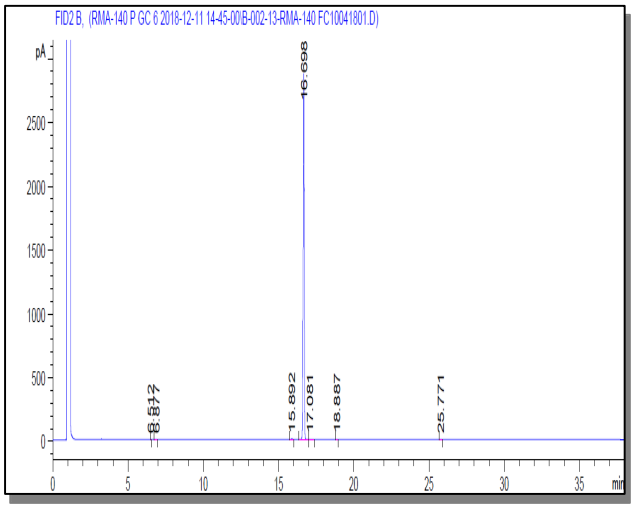
Time (min)	% A	% B
0.0	5	95
8.0	80	20
10.0	80	20
10.1	5	95

Flow Rate: 0.7 mL/min
Wavelength: 210 nm

Sample Name: FC10041801
Acquired: December 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



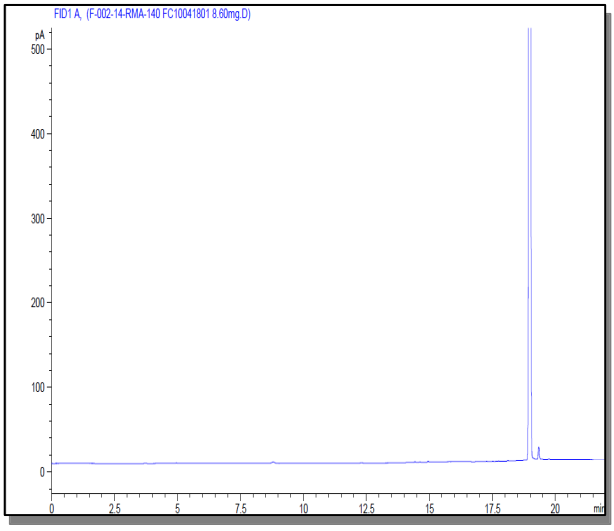
Column: DB-35ms, 30 m x 0.53 mm ID, 1.0 µm film thickness
Temp Program: 40°C to 200°C at 40°C/min
200°C to 280°C at 5°C/min
hold 18 min
Injector Temp: Cool-on-Column
Detector Temp: 325°C

Sample Name: FC10041801
Acquired: December 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

Spectral and Physical Data (cont.)

Residual Solvent Analysis by GC/FID Headspace



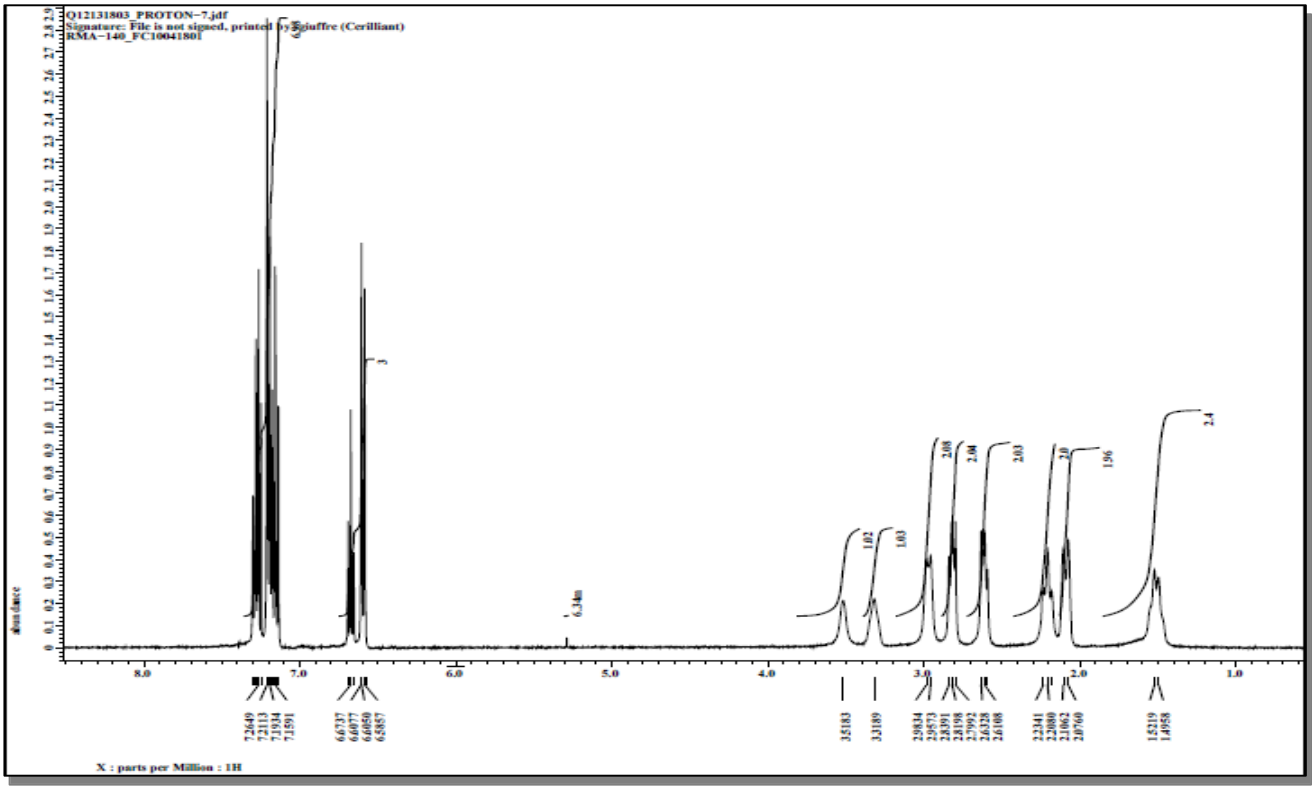
Column:	DB-ALC1 30 m x 0.53 mm, 3 µm film thickness
Temp Program:	40°C hold 12 min to 220°C at 40°C/min hold 5.5 min
Carrier Gas:	Helium
Flow Rate:	2.0 mL/min
Detector Heater Temp:	250°C
Injector:	Headspace Sampler
HS Oven Temp:	60°C
Vial Equilibration:	10 minutes
Sample Name:	FC10041801
Acquired:	December 12, 2018

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

ND - None Detected

^{1}H NMR

Instrument:	JEOL ECS 400
Solvent:	Chloroform-D



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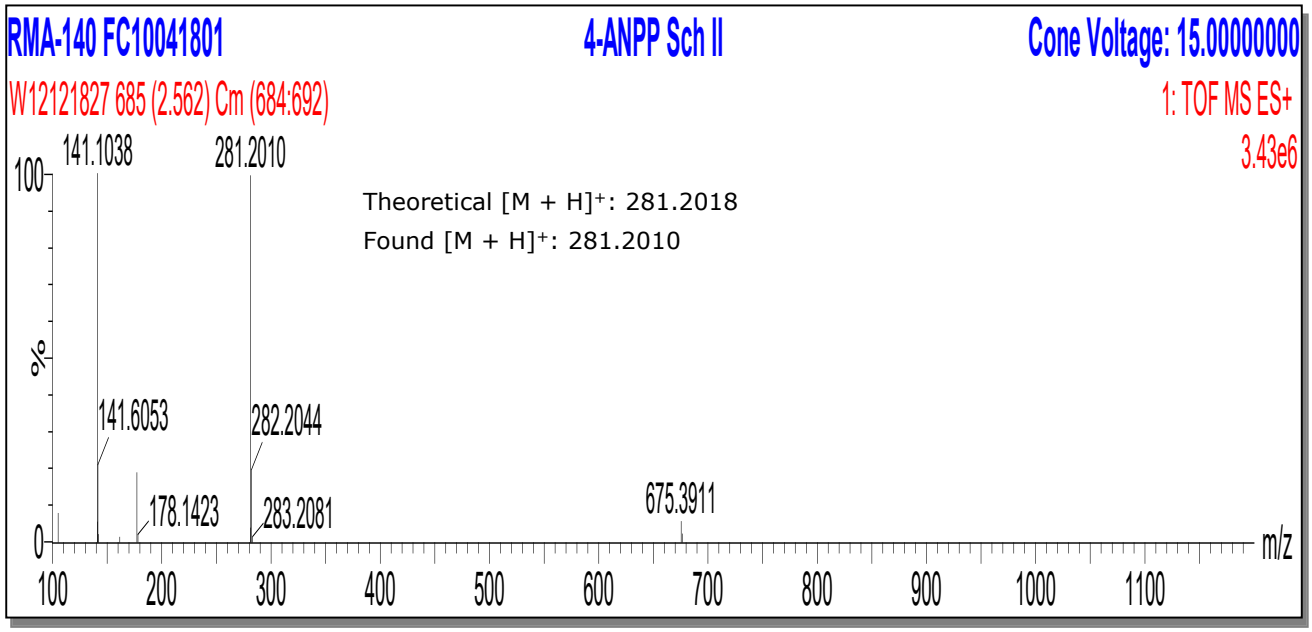
Spectral and Physical Data (cont.)

LC/MS

Column:	Ascentis Express C18, 2.7 µm, 3.0 x 50 mm	**Flow Rate:**	0.4 mL/min
Mobile Phase:	A: 0.1% Formic acid in Water B: Acetonitrile	**Scan Range:**	100-1200 amu
		Ionization:	Electrospray, Positive Ion
		Instrument:	Waters XEVO G2 QTOF
Gradient:		**Acquired:**	December 12, 2018

Time (min)	% A	% B
0.0	90	10
0.5	90	10
4.0	50	50
5.8	50	50
6.0	90	10
8.0	90	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 this product is listed below.*

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

Transport/Shipping: *Stability studies support the transport of this product at ambient conditions.*

Long Term Stability: *Long term stability has been assessed for Freezer storage (-10 °C to -25 °C) conditions. Stability of a minimum of 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	March 15, 2020	Updated Retest Date of April 2020 to February 2021.
		Added Long Term Stability.
02	December 29, 2020	Updated Retest Date of February 2021 to December 2021.

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Certified Reference Material - Certificate of Analysis

4-ANPP-$^{13}C_6$, Primary Measurement Standard

Cerilliant Quality
ISO 17034
ISO/IEC 17025
ISO 13485
ISO 14001
ISO 9001

N-Phenyl-1-(2-phenethyl)-4-piperidinamine-$^{13}C_6$

Product No.: A-175-1ML

Lot No.: FC01081902

Description of CRM: 4-ANPP-$^{13}C_6$ in Methanol (Solution)

Retest Date: October 2021 See Section "Stability Assessment".

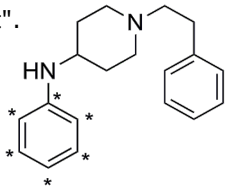
Storage: Store unopened in freezer (-10 °C to -25 °C).

Shipping: Ambient. See Section "Stability Assessment".

Chemical formula: $^{13}C_6C_{13}H_{24}N_2$

CAS No.: NA

Regulatory: USDEA Schedule II



Analyte	Certified Concentration ± associated uncertainty U, u=k*u (k=2)
4-ANPP-$^{13}C_6$	**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.
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

October 26, 2020
Issue Date

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

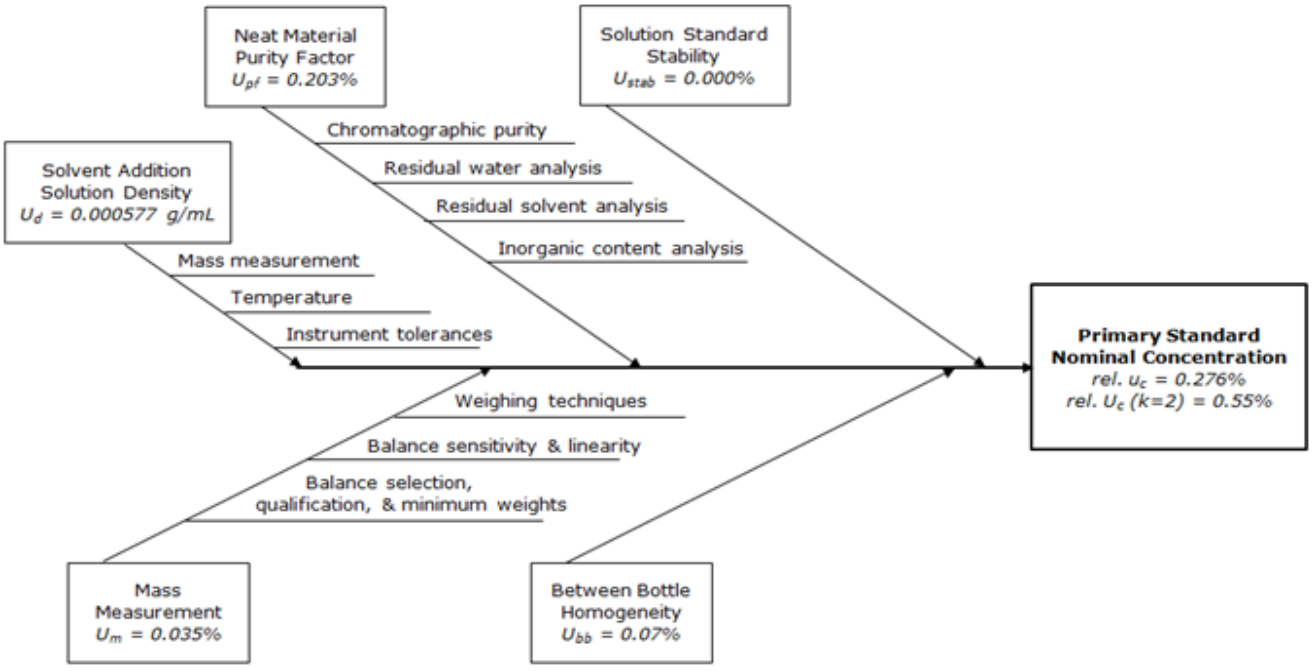
Packaging: 2 mL amber USP Type 1 glass ampoule containing not less than 1 mL of certified solution. Ampoules are overfilled to ensure a minimum of 1 mL volume can be transferred when using a 1mL Class A volumetric pipette.

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.



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Details on metrological traceability:

- This standard has been gravimetrically prepared using balances that have been fully qualified and calibrated to ISO 17025 requirements. All calibrations utilize NIST traceable weights which are calibrated externally by a qualified ISO 17025 accredited calibration laboratory to NIST standards. Qualification of each balance includes the assignment of a minimum weighing by a qualified and ISO 17025 accredited calibration vendor taking into consideration the balance and installed environmental conditions to ensure compliance with USP tolerances of NMT 0.10% relative error.
- Fill volume to predetermined specifications is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- The density and material Mass Balance Purity Factor of each raw material is traceable to the SI and higher order reference materials through mass measurement and instrument qualification and calibrations.

Details about certification process:

This standard has been prepared and certified under the ISO 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.

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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 (25:75)	**Linearity (r) :**	1.000
Flow Rate:	1.5 mL/min		
Wavelength:	210 nm		

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

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Analyte Certification - Mass Balance Purity Factor

Each analyte is thoroughly identified and characterized using an orthogonal approach. A mass balance purity factor is assigned incorporating chromatographic purity and residual impurities. The mass balance purity factor is utilized to calculate the weighing adjustment necessary to ensure accuracy of the solution standard concentration.

Material Name:	4-ANPP-$^{13}C_6$	**Chemical Formula:**	$^{13}C_6C_{13}H_{24}N_2$
Material Lot:	FC10171801	**CAS Number:**	NA
		Molecular Weight:	286.36

Material Characterization Summary

Analytical Test	**Method**	**Results**	
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 with Structure	
Isotopic Purity and Distribution by LC/MS SIM Analysis	SP10-0107	0.01% $^{13}C_0$ vs $^{13}C_6$	
		0.01% $^{13}C_0$	0.04% $^{13}C_4$
		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.

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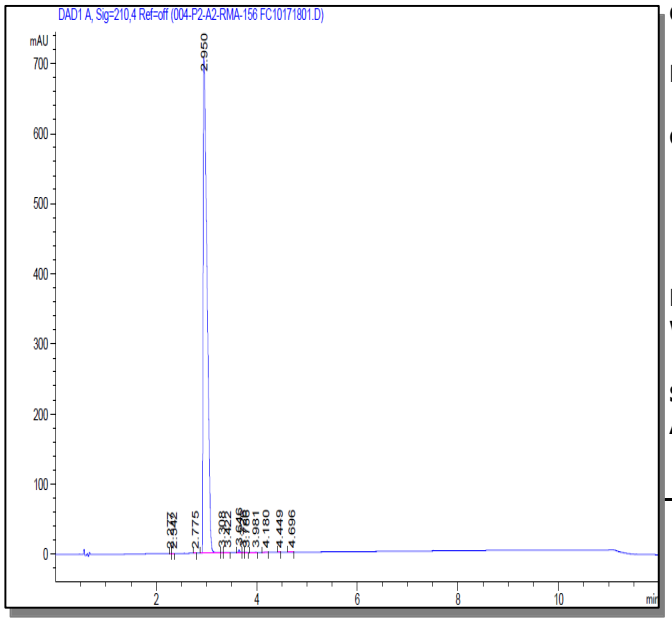
Spectral and Physical Data

HPLC/UV



Column: Ascentis Express C18, 2.7 µm, 3.0 x 100 mm

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

Gradient:

Time (min)	% A	% B
0.0	10	90
8.0	80	20
10.0	80	20
10.1	10	90

Flow Rate: 0.7 mL/min

Wavelength: 210 nm

Sample Name: FC10171801

Acquired: December 18, 2018

Peak #	Ret Time	Area %
1	2.28	0.00
2	2.34	0.00
3	2.78	0.00
4	2.95	99.69
5	3.31	0.01
6	3.42	0.03
7	3.65	0.18
8	3.73	0.02
9	3.79	0.01
10	3.98	0.01
11	4.18	0.01
12	4.45	0.01
13	4.70	0.01

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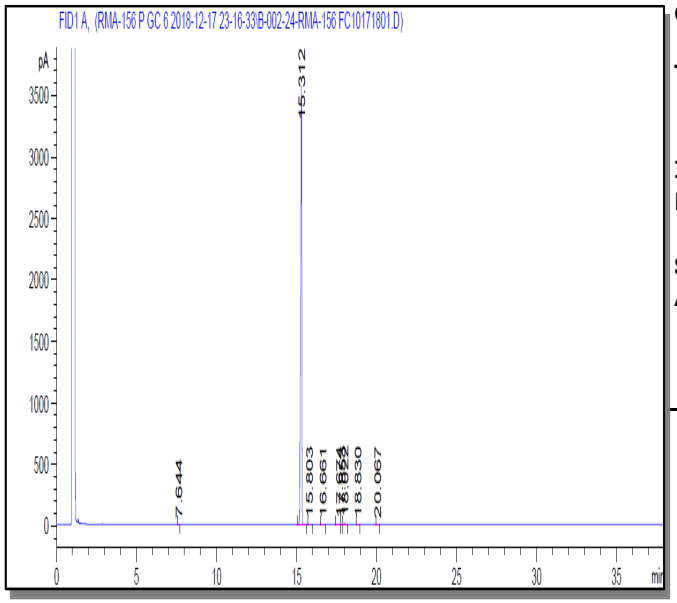
Spectral and Physical Data (cont.)

GC/FID

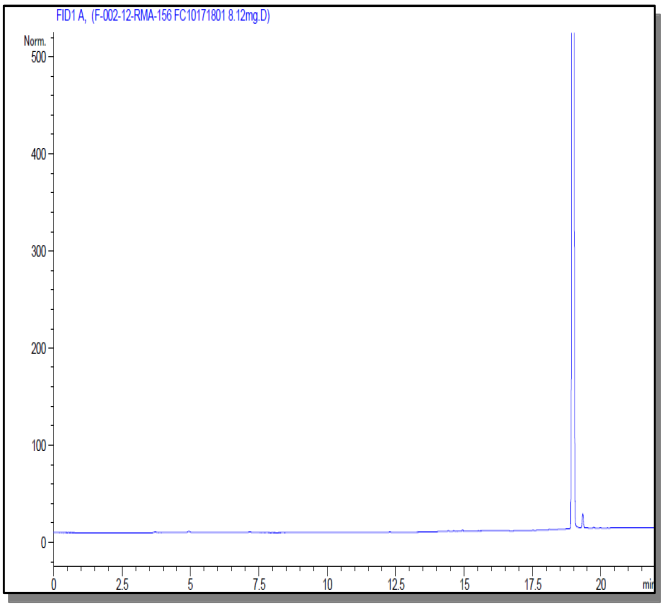


Column: DB-5ms, 30 m x 0.53 mm ID, 1.5 µm film thickness
Temp Program: 40°C to 200°C at 40°C/min
200°C to 300°C at 5°C/min
hold 16 min
Injector Temp: Cool-on-Column
Detector Temp: 325°C

Sample Name: FC10171801
Acquired: December 18, 2018

Peak #	Ret Time	Area %
1	7.64	0.00
2	15.31	99.83
3	15.80	0.00
4	16.66	0.01
5	17.67	0.01
6	17.85	0.00
7	18.02	0.14
8	18.83	0.01
9	20.07	0.00

Residual Solvent Analysis by GC/FID Headspace



Column: DB-ALC1 30 m x 0.53 mm, 3 µm film thickness
Temp Program: 40°C (12 min) to 220°C at 40°C/min (5.5 min)
Carrier Gas: Helium
Flow Rate: 2.0 mL/min
Detector Heater Temp: 250°C
Injector: Headspace Sampler
HS Oven Temp: 60°C
Vial Equilibration: 10 minutes

Sample Name: FC10171801
Acquired: December 19, 2018

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

ND - None Detected

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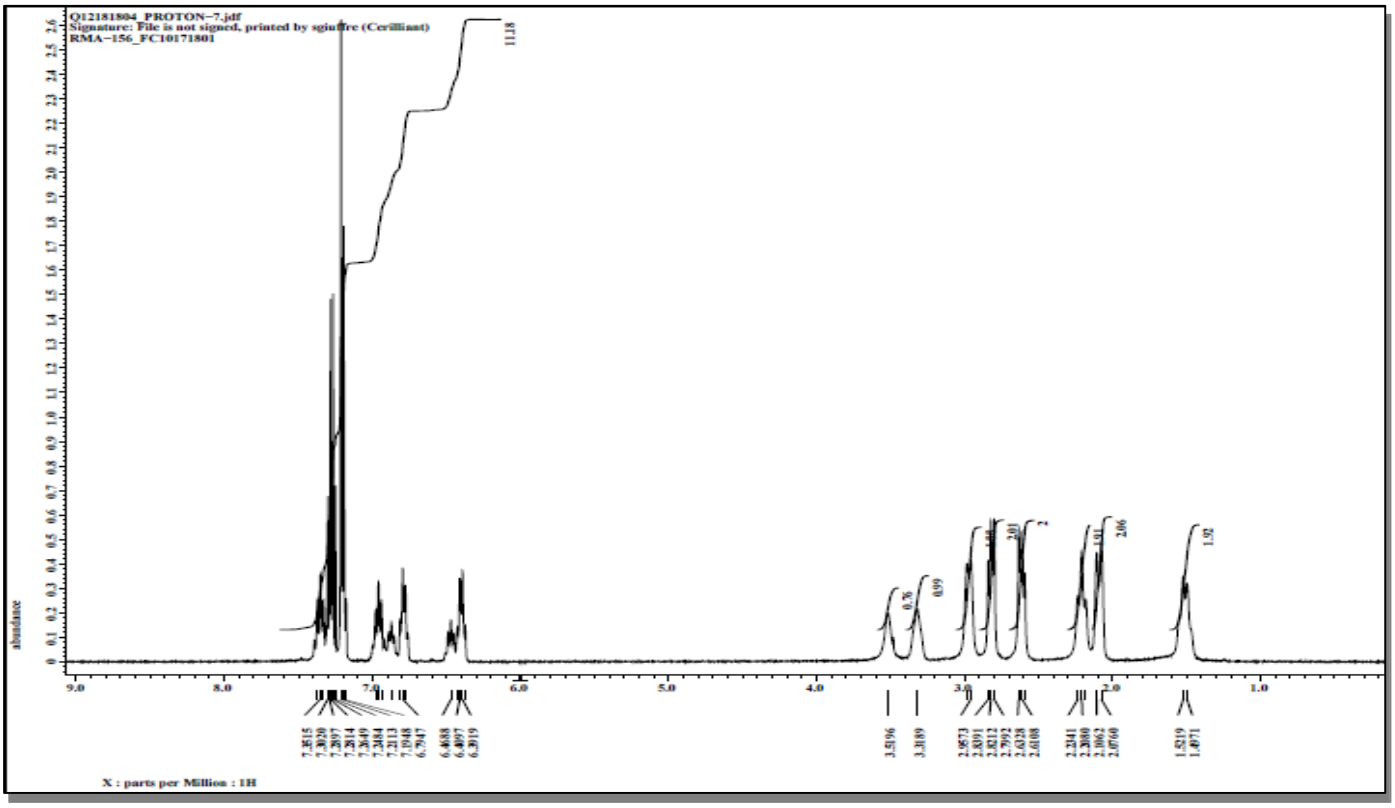
Spectral and Physical Data (cont.)

^{1}H NMR

Instrument: JEOL ECS 400
Solvent: Chloroform-D



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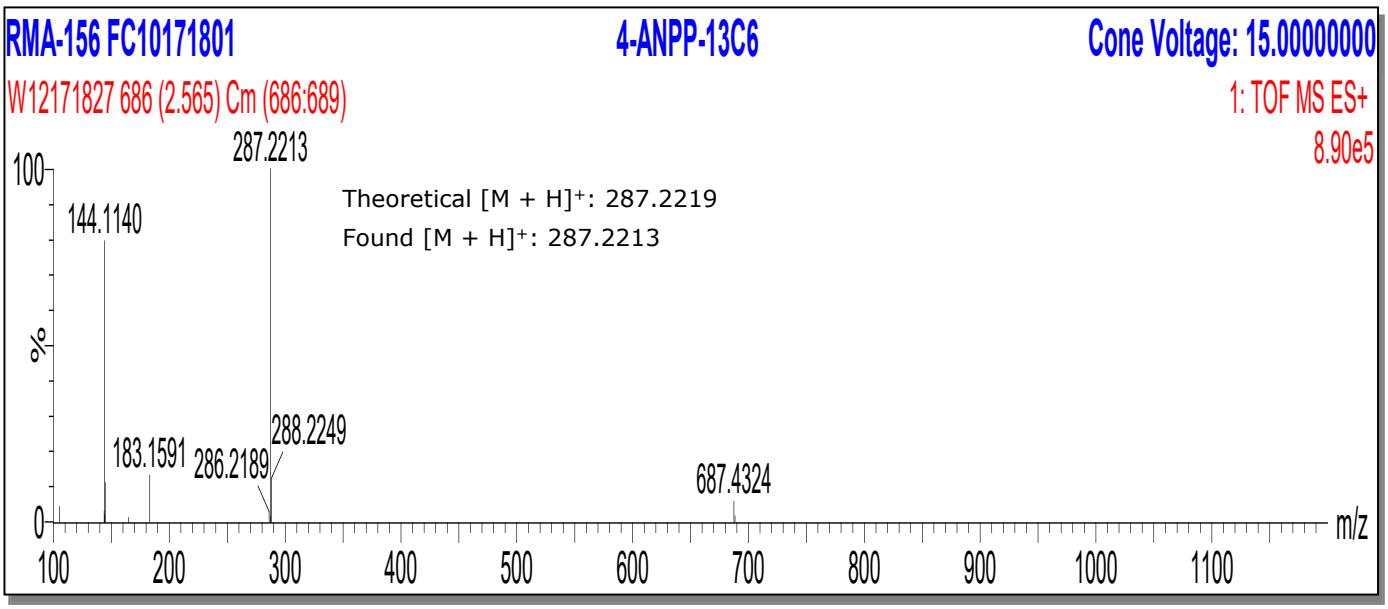
Spectral and Physical Data (cont.)

LC/MS

Column:	Ascentis Express C18, 2.7 µm, 3.0 x 50 mm	**Flow Rate:**	0.4 mL/min
Mobile Phase:	A: 0.1% Formic acid in Water B: Acetonitrile	**Scan Range:**	100-1200 amu
		Ionization:	Electrospray, Positive Ion
		Instrument:	Waters XEVO G2 QTOF
Gradient:		**Acquired:**	December 17, 2018

Time (min)	% A	% B
0.0	90	10
0.5	90	10
4.0	50	50
5.8	50	50
6.0	90	10
8.0	90	10



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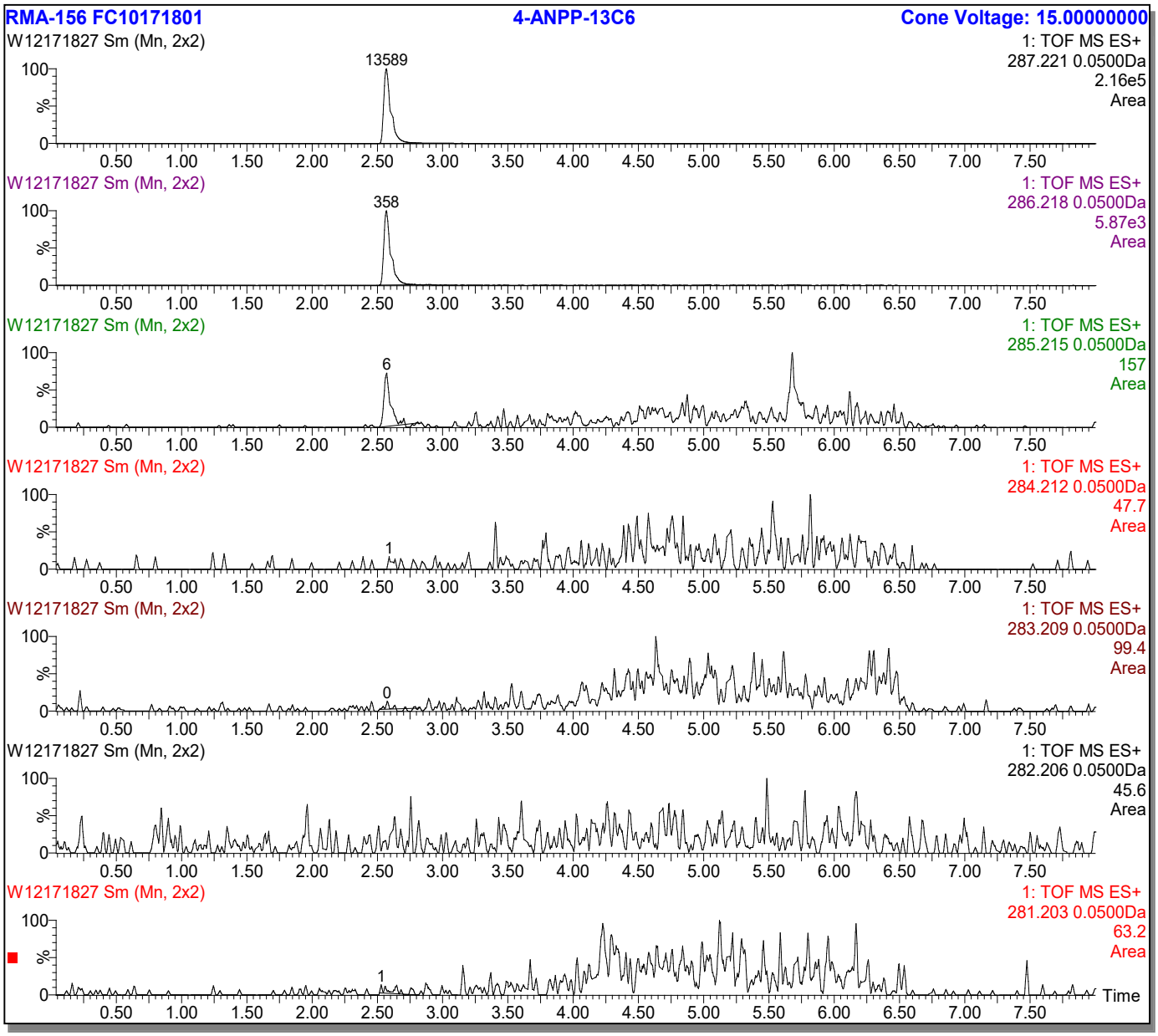
Spectral and Physical Data (cont.)

Isotopic Purity by LC/MS SIM

Column: Ascentis Express C18, 2.7 µm, 3.0 x 50 mm
Mobile Phase: A: 0.1% Formic acid in Water
B: Acetonitrile
Gradient:

Time (min)	% A	% B
0.0	90	10
0.5	90	10
4.0	50	50
5.8	50	50
6.0	90	10
8.0	90	10

Flow Rate: 0.4 mL/min
Scan Range: 281-287 amu
Ionization: Electrospray, Positive Ion
Instrument: Waters XEVO G2 QTOF
Acquired: December 17, 2018



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Stability

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

Short Term Stability: *A summary of accelerated stability findings for a related product (A-139-0.5ML, 4-ANPP) is listed below.*

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

Transport/Shipping: *Stability studies support the transport of this product at ambient conditions.*

Long Term Stability: *Long term stability has been assessed for Freezer storage (-10 °C to -25 °C) conditions. Stability of a minimum of 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.

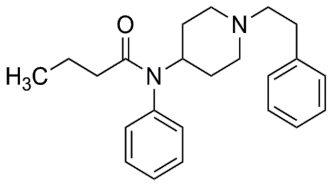
Certified Reference Material - Certificate of Analysis

Butyryl fentanyl, Primary Measurement Standard

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

Cerilliant Quality
ISO 17034
ISO/IEC 17025
ISO 13485
ISO 14001
ISO 9001

Product No.: B-083-1ML
Lot No.: FC01031904
Description of CRM: Butyryl fentanyl in Methanol (Solution)
Retest Date: November 2021 See Section "Stability Assessment".
Storage: Store unopened in freezer (-10 °C to -25 °C).
Shipping: Ambient. See Section "Stability Assessment".
Chemical formula: $C_{23}H_{30}N_2O$
CAS No.: 1169-70-6
Regulatory: USDEA Schedule I



Analyte	Certified Concentration ± associated uncertainty U, u=k*u (k=2)
Butyryl 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 µL for quantitative applications

Instructions for handling and correct use: Concentration is corrected for chromatographic purity, residual water, residual solvents and residual inorganics. No adjustment required before use. Users should quantitatively transfer desired volume using established good laboratory practices to spike into matrix or to dilute to the desired concentration. Each ampoule is intended for one-time use.

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

Accreditation: Cerilliant Corp. is accredited by the US accreditation authority ANAB as registered reference material producer AR-1353 in accordance with ISO 17034 and registered testing laboratory AT-1352 according to ISO/IEC 17025.

Darron Ellsworth, Quality Assurance Manager

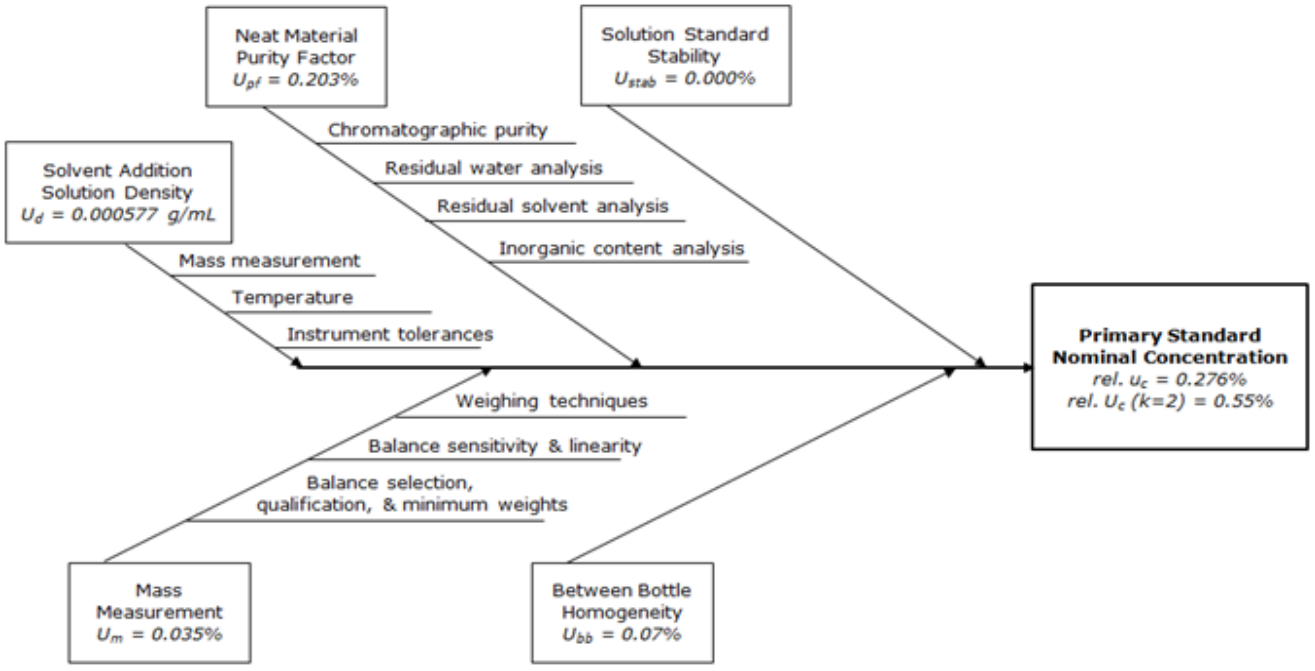
December 14, 2020
Issue Date

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.



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Details on metrological traceability:

- This standard has been gravimetrically prepared using balances that have been fully qualified and calibrated to ISO 17025 requirements. All calibrations utilize NIST traceable weights which are calibrated externally by a qualified ISO 17025 accredited calibration laboratory to NIST standards. Qualification of each balance includes the assignment of a minimum weighing by a qualified and ISO 17025 accredited calibration vendor taking into consideration the balance and installed environmental conditions to ensure compliance with USP tolerances of NMT 0.10% relative error.
- Fill volume to predetermined specifications is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- The density and material Mass Balance Purity Factor of each raw material is traceable to the SI and higher order reference materials through mass measurement and instrument qualification and calibrations.

Details about certification process:

This standard has been prepared and certified under the ISO 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.

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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 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 (mg/mL)	**%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.

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Analyte Certification - Mass Balance Purity Factor

Each analyte is thoroughly identified and characterized using an orthogonal approach. A mass balance purity factor is assigned incorporating chromatographic purity and residual impurities. The mass balance purity factor is utilized to calculate the weighing adjustment necessary to ensure accuracy of the solution standard concentration.

Material Name:	Butyryl fentanyl	**Chemical Formula:**	$C_{23}H_{30}N_2O$
Material Lot:	FC12111801	**CAS Number:**	1169-70-6
		Molecular Weight:	350.50

Material Characterization Summary

Analytical Test	**Method**	**Results**
Primary Chromatographic Purity by HPLC/UV Analysis	SP10-0102	99.8%
Secondary Chromatographic Purity by GC/FID Analysis	SP10-0106	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.

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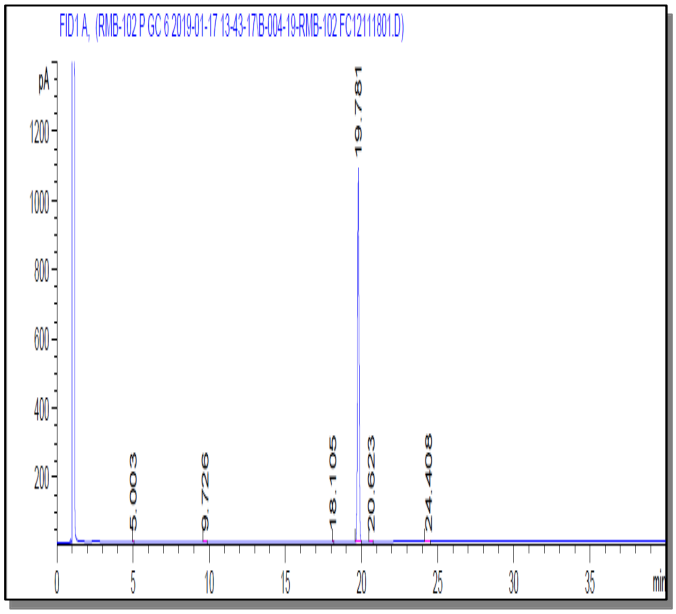
Spectral and Physical Data

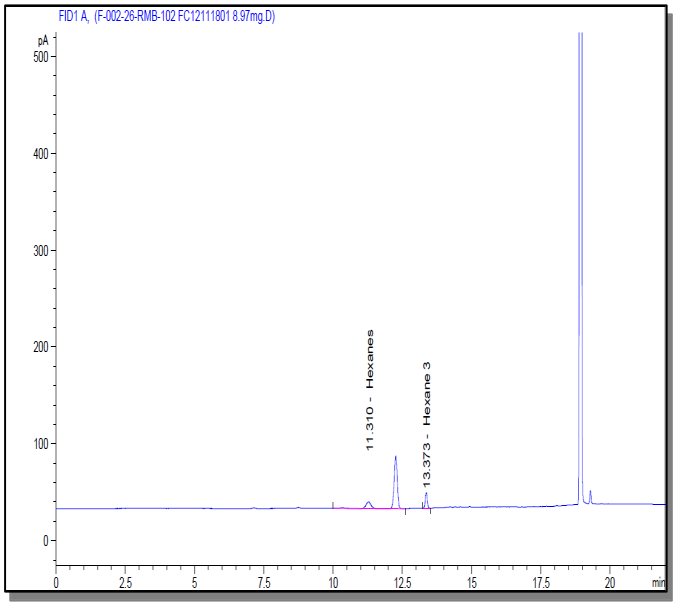
GC/FID



Column:	DB-35ms, 30 m x 0.53 mm ID, 1.0 µm film thickness
Temp Program:	40°C to 200°C at 40°C/min 200°C to 300°C at 5°C/min hold 16 min
Injector Temp:	Cool-on-Column
Detector Temp:	325°C
Sample Name:	FC12111801
Acquired:	January 17, 2019

Peak #	Ret Time	Area %
1	5.00	0.02
2	9.73	0.09
3	18.11	0.01
4	19.78	99.83
5	20.62	0.01
6	24.41	0.04

Residual Solvent Analysis by GC/FID Headspace



Column:	DB-ALC1 30 m x 0.53 mm, 3 µm film thickness
Temp Program:	40°C 12 min to 220°C at 40°C/min 5.5 min
Carrier Gas:	Helium
Flow Rate:	2.0 mL/min
Detector Heater Temp:	250°C
Injector:	Headspace Sampler
HS Oven Temp:	60°C
Vial Equilibration:	10 minutes
Sample Name:	FC12111801
Acquired:	January 23, 2019

Peak	Compound	Area	Weight %
1	Hexanes	585.95	0.16
2	NMP	NA	NA
Total			**0.16**

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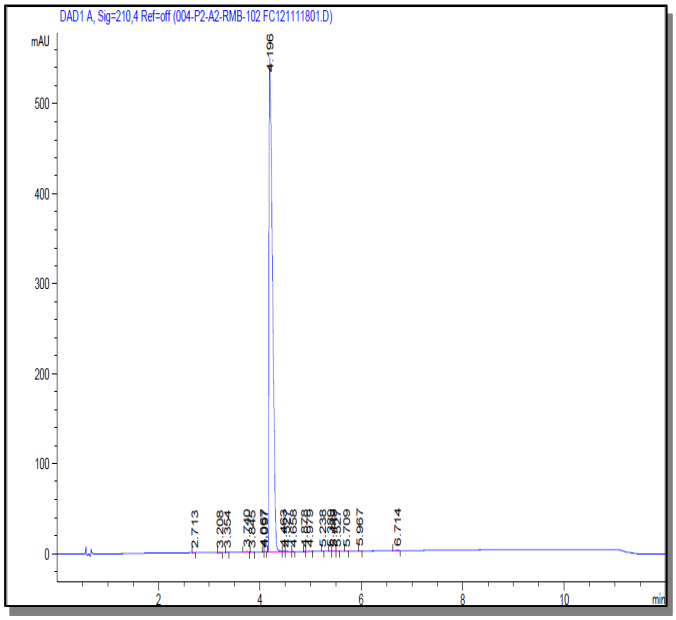
Spectral and Physical Data (cont.)

HPLC/UV



Column: Ascentis Express C18, 2.7 µm, 3.0 x 100 mm

Mobile Phase: A: Acetonitrile
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/min

Wavelength: 210 nm

Sample Name: FC12111801

Acquired: January 16, 2019

Peak #	Ret 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	5.71	0.01
19	5.97	0.01
20	6.71	0.09

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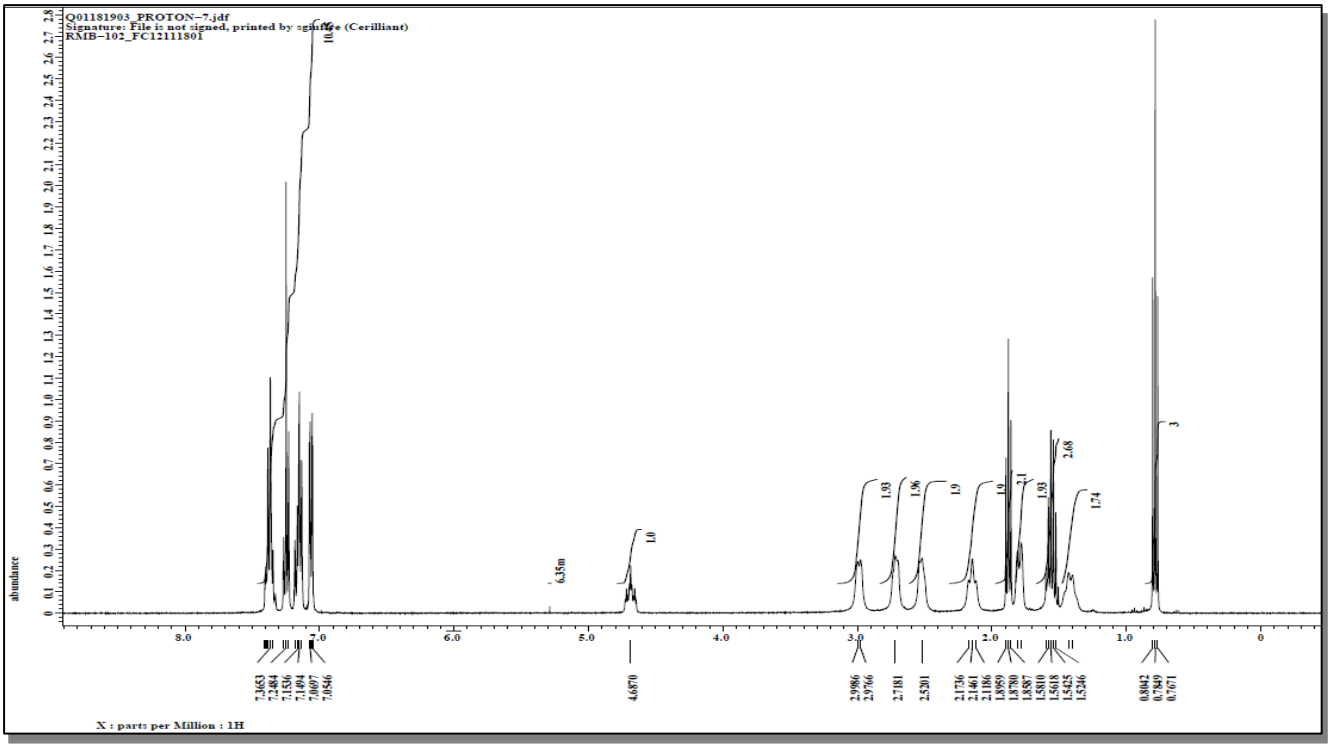
Spectral and Physical Data (cont.)

^{1}H NMR

Instrument: JEOL ECS 400
Solvent: Chloroform-D



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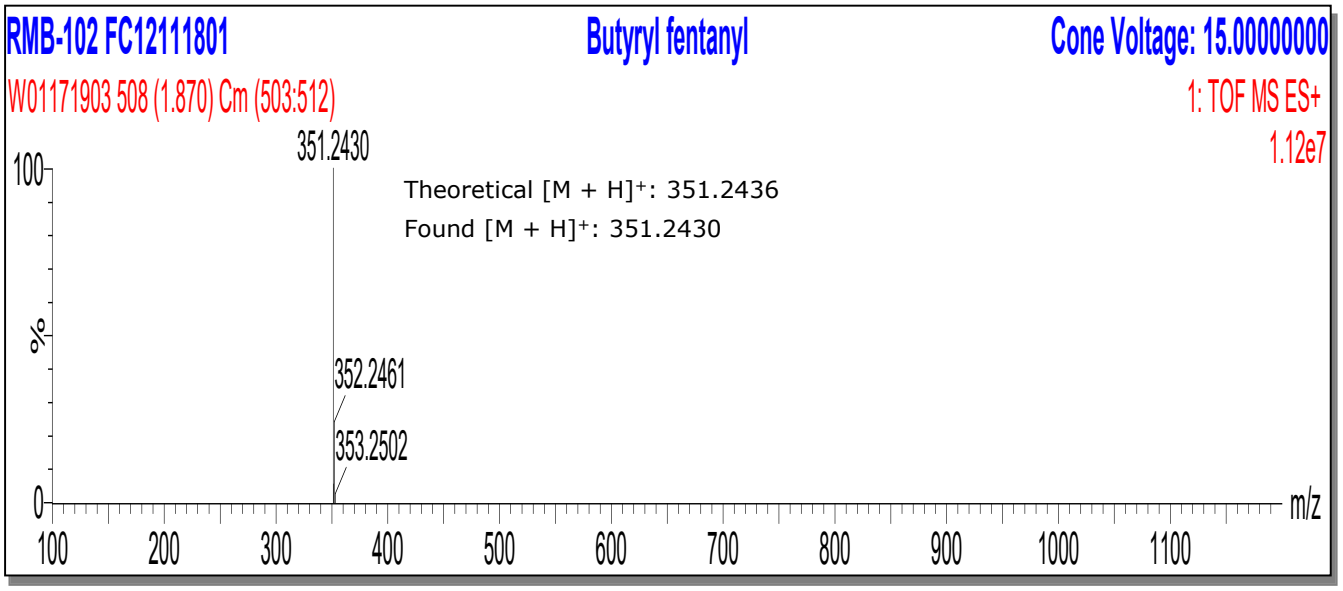
Spectral and Physical Data (cont.)

LC/MS

Column:	Ascentis Express C18, 2.7 µm, 3.0 x 50 mm	**Flow Rate:**	0.4 mL/min
Mobile Phase:	A: 0.1% Formic acid in Water	**Scan Range:**	100-1200 amu
	B: Acetonitrile	**Ionization:**	Electrospray, Positive Ion
Gradient:		**Instrument:**	Waters XEVO G2 QTOF
		Acquired:	January 17, 2019

Time (min)	% A	% B
0.0	80	20
0.5	80	20
4.0	20	80
5.8	20	80
6.0	80	20
8.0	80	20



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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 this product is listed below.*

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

Transport/Shipping: *Stability studies support the transport of this product at ambient conditions.*

Long Term Stability: *Long term stability has been assessed for Freezer storage (-10 °C to -25 °C) conditions. Stability of a minimum of 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 13, 2019	Initial version.
01	February 18, 2020	Revised Retest Date from April 2020 to February 2021.
		Added Long Term Stability section.
02	December 14, 2020	Revised Retest Date from February 2021 to November 2021.

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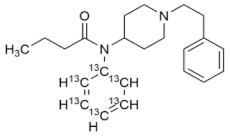
Certified Reference Material - Certificate of Analysis

Butyryl fentanyl-$^{13}C_6$, Primary Measurement Standard

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

Cerilliant Quality
ISO 17034
ISO/IEC 17025
ISO 13485
ISO 14001
ISO 9001

Product No.: B-084-1ML
Lot No.: FC01141903
Description of CRM: Butyryl fentanyl-$^{13}C_6$ in Methanol (Solution)
Retest Date: November 2021 See Section "Stability Assessment".
Storage: Store unopened in freezer (-10 °C to -25 °C).
Shipping: Ambient. See Section "Stability Assessment".
Chemical formula: $C_{17}{}^{13}C_6H_{30}N_2O$
CAS No.: NA
Regulatory: USDEA Schedule I



Analyte	Certified Concentration ± associated uncertainty U, u=k*u (k=2)
Butyryl 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.
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

December 14, 2020
Issue Date

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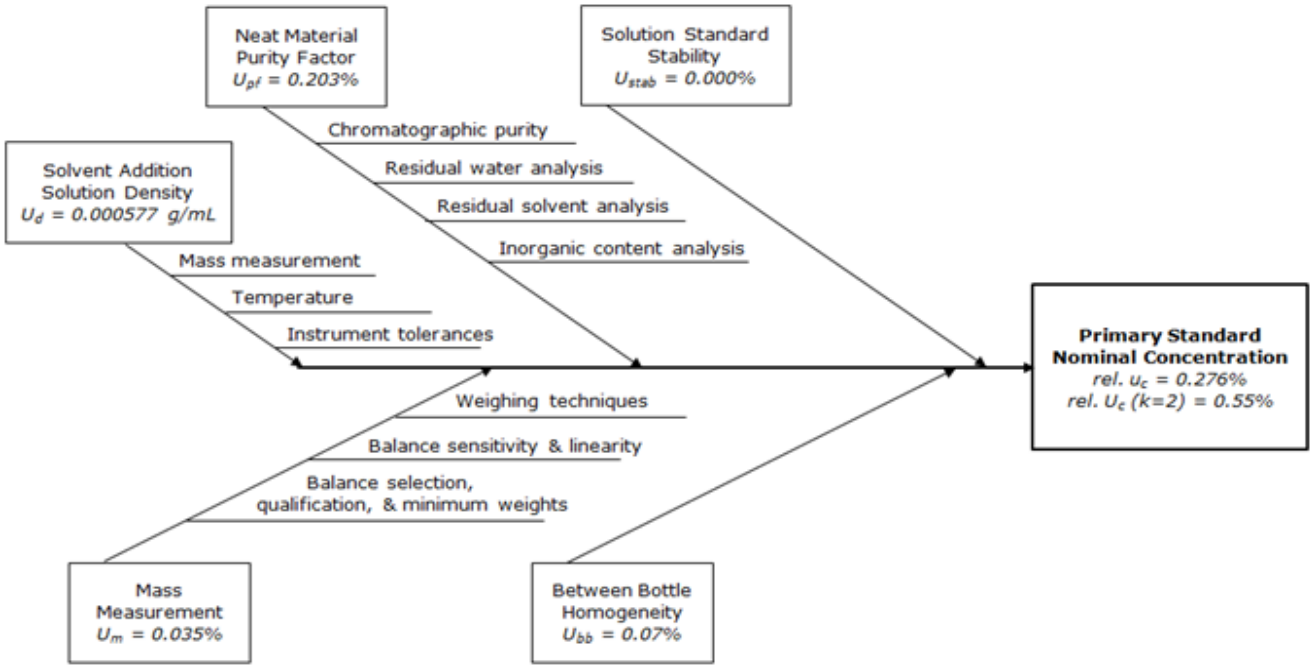
Packaging:	2 mL amber USP Type 1 glass ampoule containing not less than 1 mL of certified solution. Ampoules are overfilled to ensure a minimum of 1 mL volume can be transferred when using a 1mL Class A volumetric pipette.
Details on starting materials:	Each raw material utilized has been identified 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.



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Details on metrological traceability:

- This standard has been gravimetrically prepared using balances that have been fully qualified and calibrated to ISO 17025 requirements. All calibrations utilize NIST traceable weights which are calibrated externally by a qualified ISO 17025 accredited calibration laboratory to NIST standards. Qualification of each balance includes the assignment of a minimum weighing by a qualified and ISO 17025 accredited calibration vendor taking into consideration the balance and installed environmental conditions to ensure compliance with USP tolerances of NMT 0.10% relative error.
- Fill volume to predetermined specifications is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- The density and material Mass Balance Purity Factor of each raw material is traceable to the SI and higher order reference materials through mass measurement and instrument qualification and calibrations.

Details about certification process:

This standard has been prepared and certified under the ISO 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.

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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 (mg/mL)	**%RSD - Homogeneity**
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.

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Analyte Certification - Mass Balance Purity Factor

Each analyte is thoroughly identified and characterized using an orthogonal approach. A mass balance purity factor is assigned incorporating chromatographic purity and residual impurities. The mass balance purity factor is utilized to calculate the weighing adjustment necessary to ensure accuracy of the solution standard concentration.

Material Name:	Butyryl fentanyl-$^{13}C_6$	**Chemical Formula:**	$C_{17}{}^{13}C_6H_{30}N_2O$
Material Lot:	FC10091802	**CAS Number:**	NA
		Molecular Weight:	356.45

Material Characterization Summary

Analytical Test	**Method**	**Results**	
Primary Chromatographic Purity by HPLC/UV Analysis	SP10-0102	99.1%	
Secondary Chromatographic Purity by LC/MS Analysis	SP10-0107	98.9%	
Identity by LC/MS Analysis	SP10-0107	Consistent with Structure	
Isotopic Purity and Distribution by LC/MS SIM Analysis	SP10-0107	0.01% $^{13}C_0$ vs $^{13}C_6$	
		0.01% $^{13}C_0$	0.05% $^{13}C_4$
		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 Analysis	USP <761>, SP10-0116	Consistent with Structure	
Residual Solvent Analysis 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 Factor		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.

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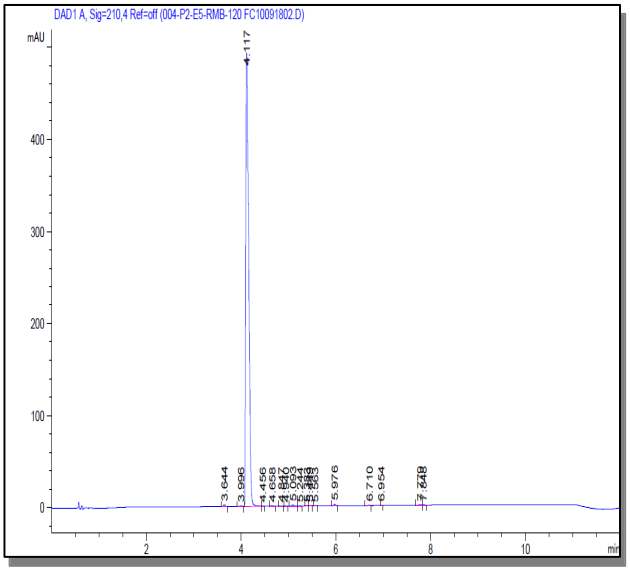
Spectral and Physical Data

HPLC/UV



Column: Ascentis Express C18, 2.7 µm 3.0 x 100 mm

Mobile Phase: A: Acetonitrile
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/min

Wavelength: 210 nm

Sample Name: FC10091802

Acquired: December 12, 2018

Peak #	Ret Time	Area %
1	3.64	0.23
2	4.00	0.08
3	4.12	99.06
4	4.46	0.03
5	4.66	0.06
6	4.85	0.02
7	4.94	0.02
8	5.09	0.14
9	5.24	0.01
10	5.38	0.01
11	5.45	0.01
12	5.56	0.02
13	5.98	0.18
14	6.71	0.01
15	6.95	0.01
16	7.78	0.08
17	7.85	0.02

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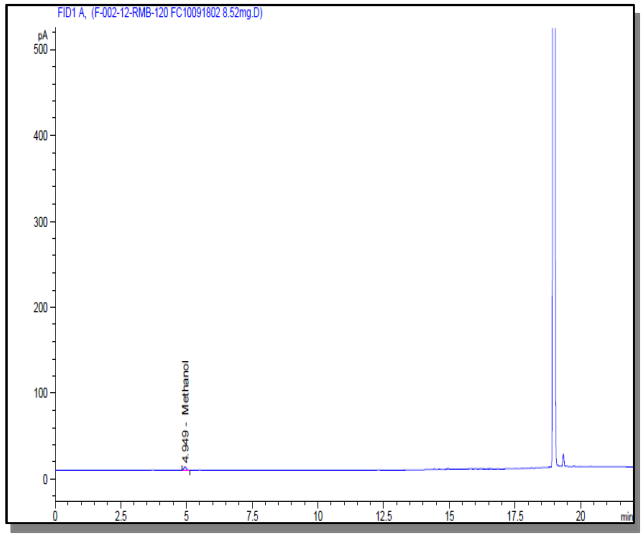
Spectral and Physical Data (cont.)

Residual Solvent Analysis by GC/FID Headspace

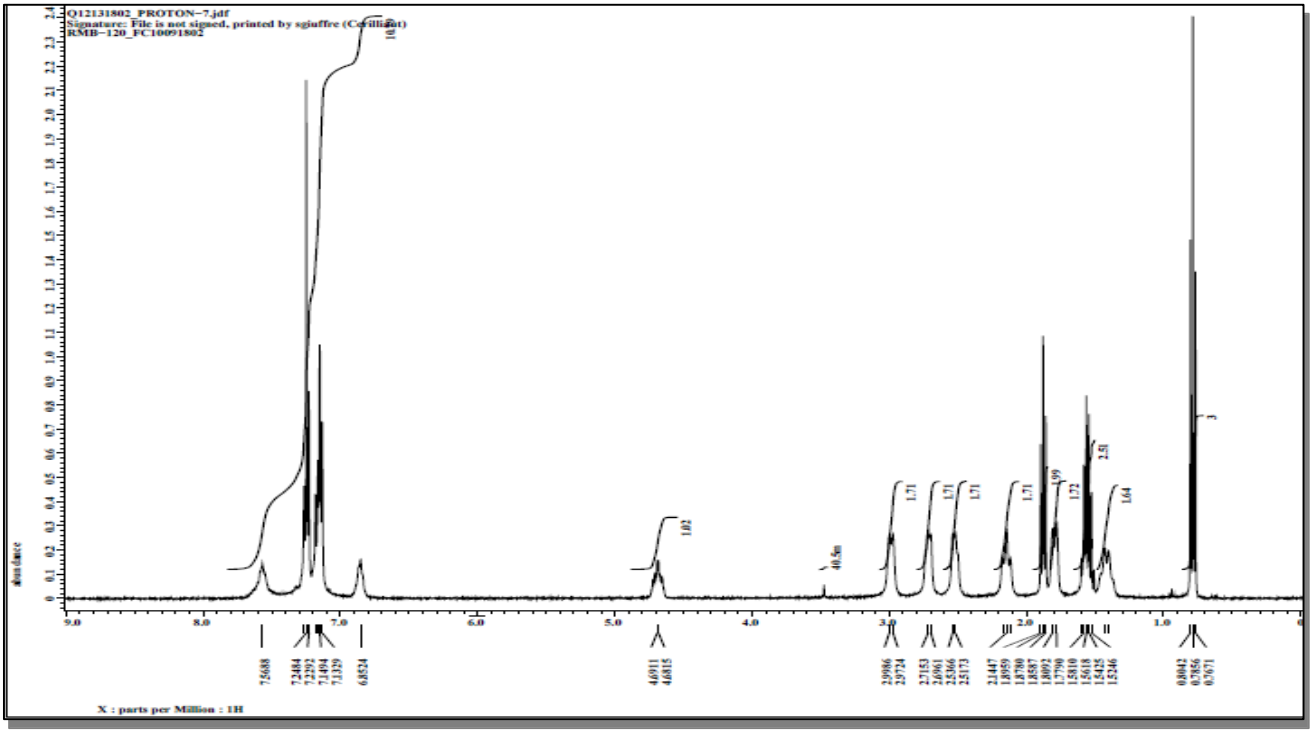


Column:	DB-ALC1 30 m x 0.53 mm, 3 µm film thickness
Temp Program:	40°C hold 12 min to 220°C at 40°C/min hold 5.5 min
Carrier Gas:	Helium
Flow Rate:	2.0 mL/min
Detector Heater Temp:	250°C
Injector:	Headspace Sampler
HS Oven Temp:	60°C
Vial Equilibration:	10 minutes
Sample Name:	FC10091802
Acquired:	December 12, 2018

Peak	Compound	Area	Weight %
1	Methanol	24.62	0.25
2	NMP	NA	NA
Total			**0.25**

^{1}H NMR

Instrument:	JEOL ECS 400
Solvent:	Chloroform-D



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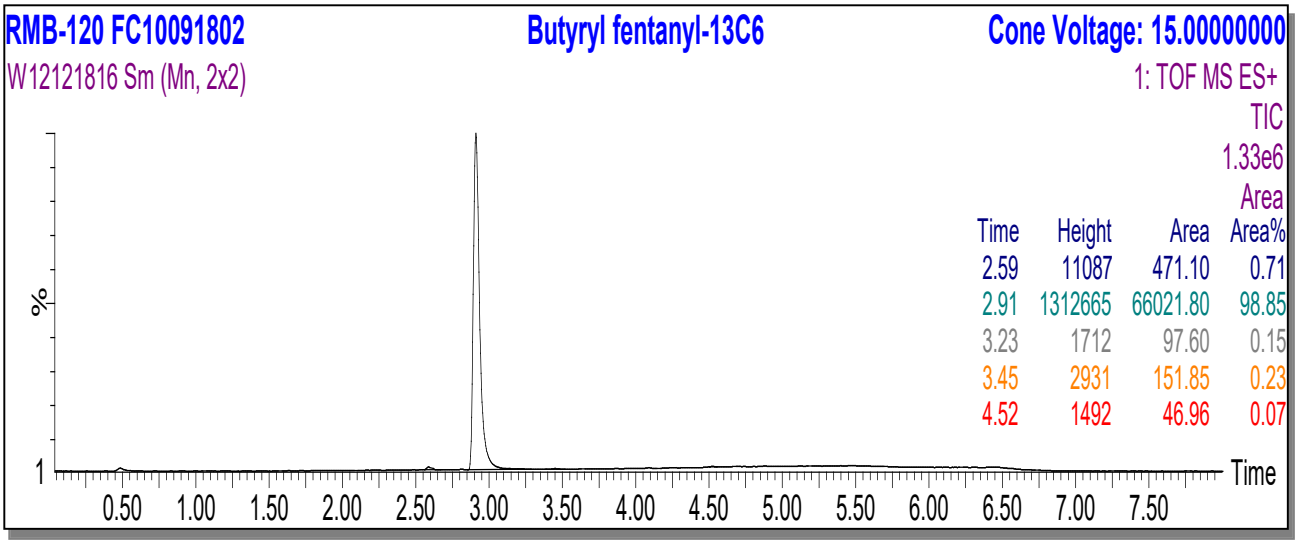
Spectral and Physical Data (cont.)

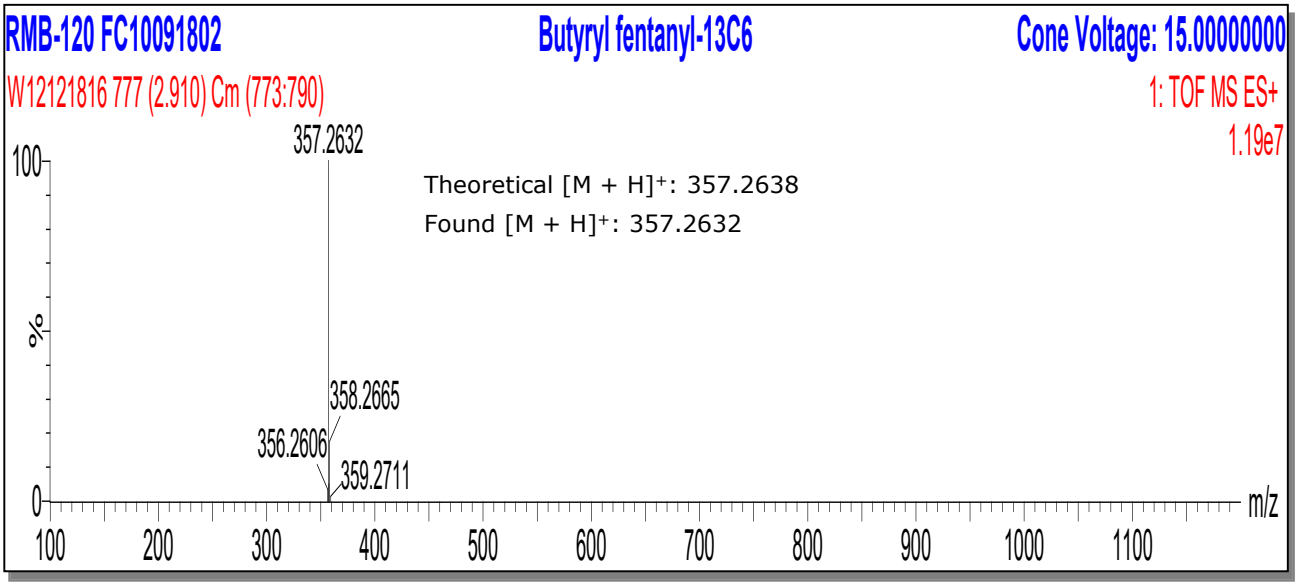
LC/MS

Column:	Ascentis Express C18, 2.7 µm, 3.0 x 50 mm
Mobile Phase:	A: 0.1% Formic acid in Water B: Acetonitrile
Gradient:	

Time (min)	% A	% B
0.0	90	10
0.5	90	10
4.0	50	50
5.8	50	50
6.0	90	10
8.0	90	10

Flow Rate:	0.4 mL/min
Scan Range:	100-1200 amu
Ionization:	Electrospray, Positive Ion
Instrument:	Waters XEVO G2 QTOF
Acquired:	December 12, 2018





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Spectral and Physical Data (cont.)

Isotopic Purity by LC/MS SIM

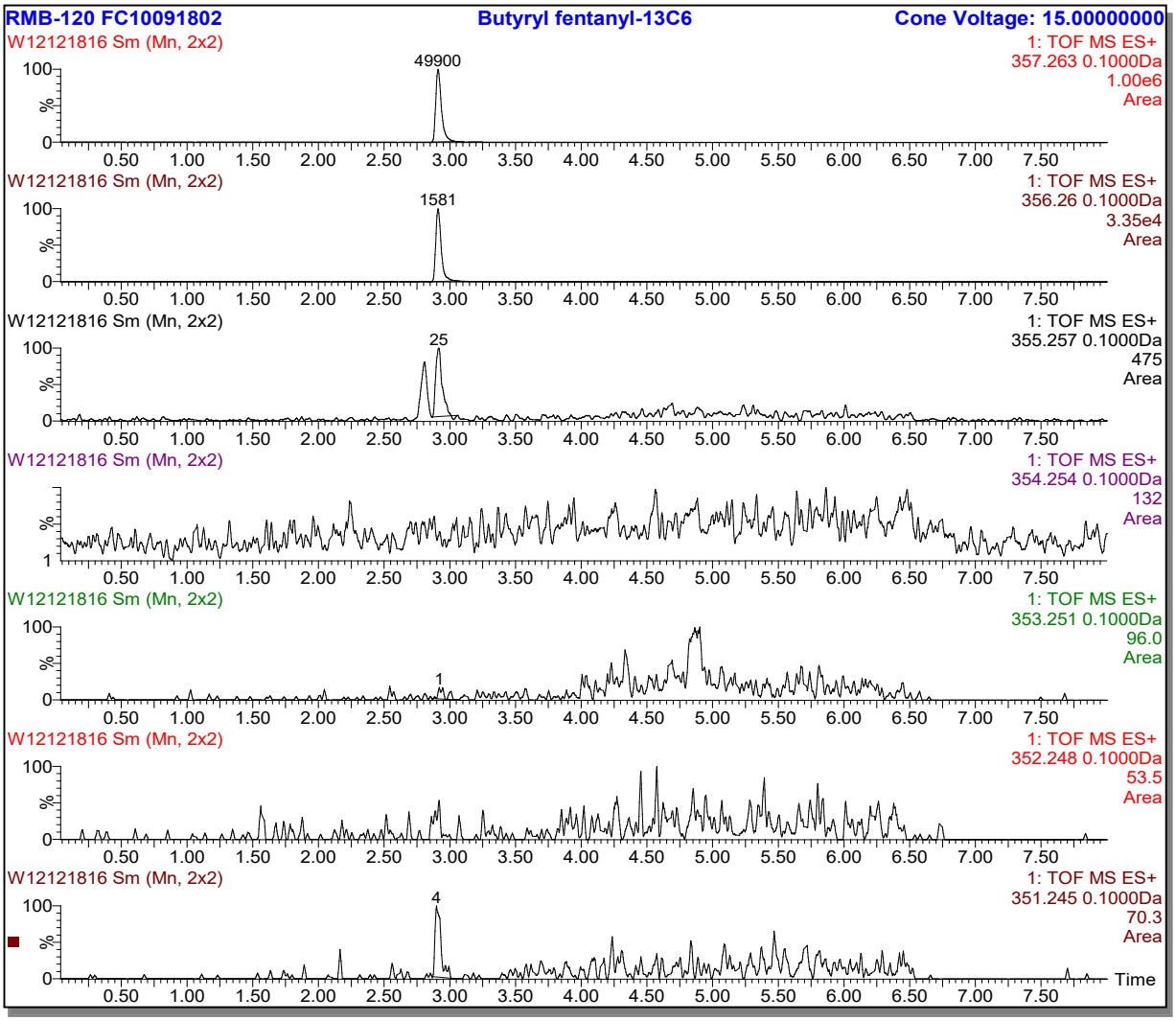
Column: Ascentis Express C18, 2.7 µm, 3.0 x 50 mm

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

Gradient:

Time (min)	% A	% B
0.0	90	10
0.5	90	10
4.0	50	50
5.8	50	50
6.0	90	10
8.0	90	10

Flow Rate: 0.4 mL/min
Scan Range: 351-357 amu
Ionization: Electrospray, Positive Ion
Instrument: Waters XEVO G2 QTOF
Acquired: December 12, 2018



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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 (B-066-0.5ML, Butyryl fentanyl) is listed below.*

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

Transport/Shipping: *Stability studies support the transport of this product at ambient conditions.*

Long Term Stability: *Long term stability has been assessed for Freezer storage (-10 °C to -25 °C) conditions. Stability of a minimum of 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	February 18, 2020	Revised Retest Date from April 2020 to February 2021.
		Added Long Term Stability section.
02	December 14, 2020	Revised Retest Date from February 2021 to November 2021.
		Added chemical structure to first page.

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

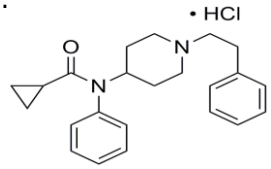
Certified Reference Material - Certificate of Analysis

Cyclopropyl fentanyl, Primary Measurement Standard

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

Cerilliant Quality
ISO 17034
ISO/IEC 17025
ISO 13485
ISO 14001
ISO 9001

Product No.: C-198-1ML
Lot No.: FC12261807
Description of CRM: Cyclopropyl fentanyl HCl in Methanol (Solution)
Nominal concentration is adjusted for HCl content.
Retest Date: November 2021 See Section "Stability Assessment".
Storage: Store unopened in freezer (-10 °C to -25 °C).
Shipping: Ambient. See Section "Stability Assessment".
Chemical formula: $C_{23}H_{28}N_2O$ • HCl
CAS No.: NA
Regulatory: USDEA Schedule I



Analyte	Certified Concentration ± associated uncertainty U, u=k*u (k=2)
Cyclopropyl 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 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 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.

ANAB ACCREDITED ISO 17034 REFERENCE MATERIAL PRODUCER

Darren Ellsworth, Quality Assurance Manager

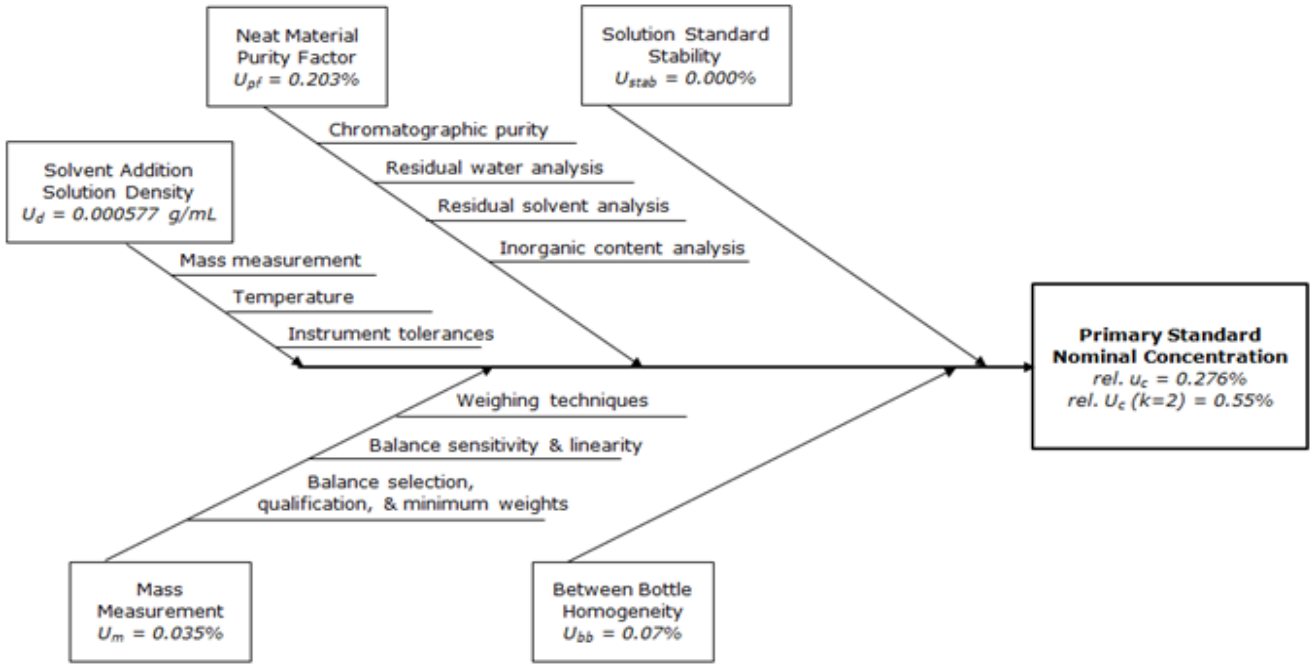
January 11, 2021
Issue Date

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.



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Details on metrological traceability:

- This standard has been gravimetrically prepared using balances that have been fully qualified and calibrated to ISO 17025 requirements. All calibrations utilize NIST traceable weights which are calibrated externally by a qualified ISO 17025 accredited calibration laboratory to NIST standards. Qualification of each balance includes the assignment of a minimum weighing by a qualified and ISO 17025 accredited calibration vendor taking into consideration the balance and installed environmental conditions to ensure compliance with USP tolerances of NMT 0.10% relative error.
- Fill volume to predetermined specifications is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- The density and material Mass Balance Purity Factor of each raw material is traceable to the SI and higher order reference materials through mass measurement and instrument qualification and calibrations.

Details about certification process:

This standard has been prepared and certified under the ISO 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:	1.7 mL/min		
Wavelength:	210 nm		

		Verified Concentration (mg/mL)	**%RSD - 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.

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Analyte Certification - Mass Balance Purity Factor

Each analyte is thoroughly identified and characterized using an orthogonal approach. A mass balance purity factor is assigned incorporating chromatographic purity and residual impurities. The mass balance purity factor and salt adjustment are utilized to calculate the weighing adjustment necessary to ensure accuracy of the solution standard concentration.

Material Name:	Cyclopropyl fentanyl HCl	**Molecular Weight (base):**	348.48
Material Lot:	FC10031801	**Molecular Weight (salt):**	384.94
Chemical Formula:	$C_{23}H_{28}N_2O$ • HCl	**Salt Adjustment:**	1.105
CAS Number:	NA		

Material Characterization 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% [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 Microash Analysis	SP10-0135	< 0.2%		
Elemental Analysis	Outsourced		Calculated	Analyzed
		C	71.76%	71.59%
		H	7.59%	7.61%
		N	7.28%	7.45%
Mass Balance Purity Factor		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.

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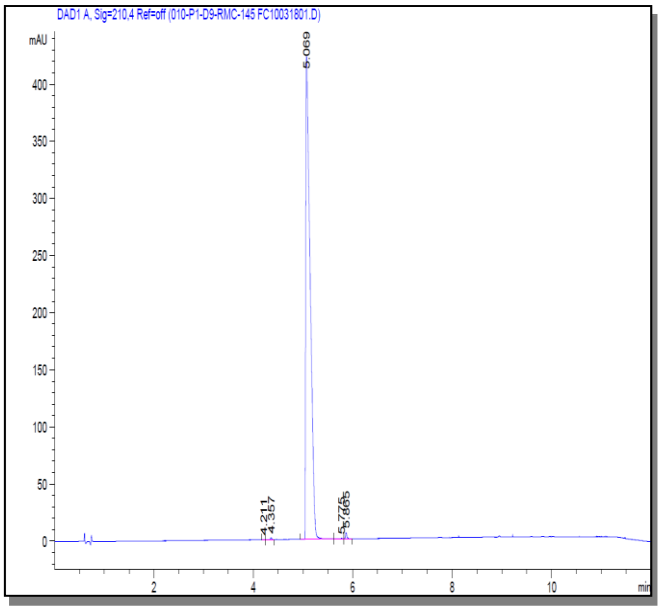
Spectral and Physical Data

HPLC/UV



Column: Ascentis Express Phenyl-Hexyl, 2.7 µm, 3.0 x 100 mm

Mobile Phase: A: Acetonitrile
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/min

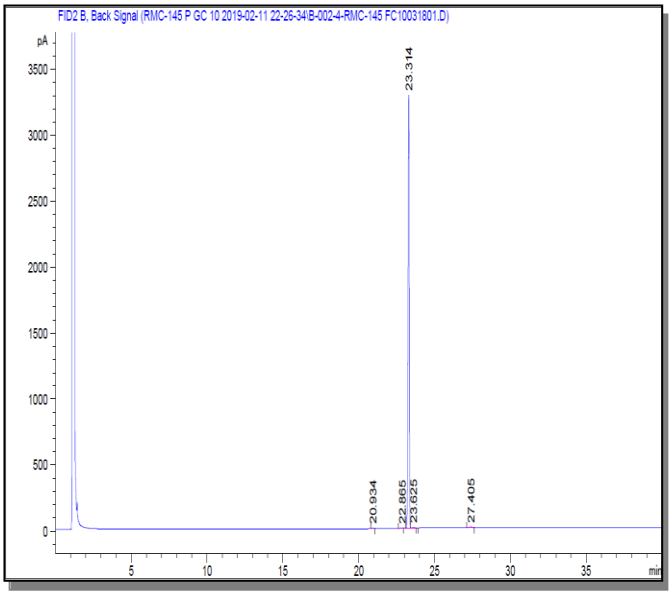
Wavelength: 210 nm

Sample Name: FC10031801

Acquired: February 11, 2019

Peak #	Ret Time	Area %
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



Column: DB-35ms, 30 m x 0.53 mm ID, 1.0 µm film thickness

Temp Program: 40°C to 200°C at 40°C/min
200°C to 300°C at 5°C/min hold 16 min

Injector Temp: Cool-on-Column

Detector Temp: 325°C

Sample Name: FC10031801

Acquired: February 11, 2019

Peak #	Ret Time	Area %
1	20.93	0.10
2	22.87	0.03
3	23.31	99.31
4	23.63	0.21
5	27.41	0.35

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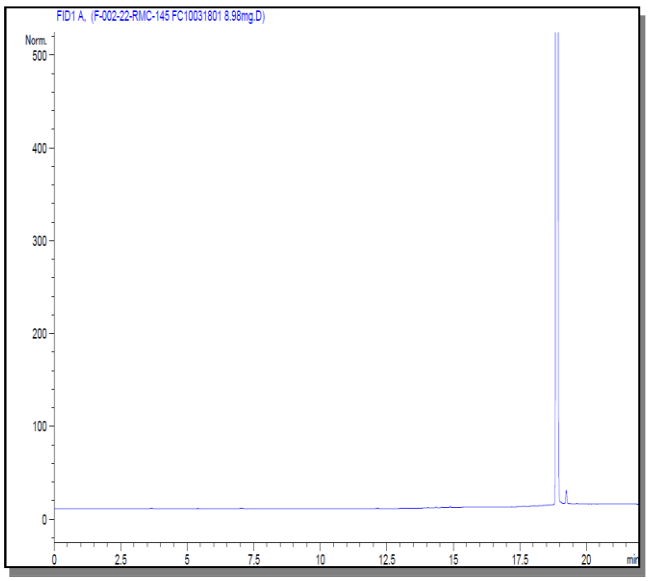
Spectral and Physical Data (cont.)

Residual Solvent Analysis by GC/FID Headspace



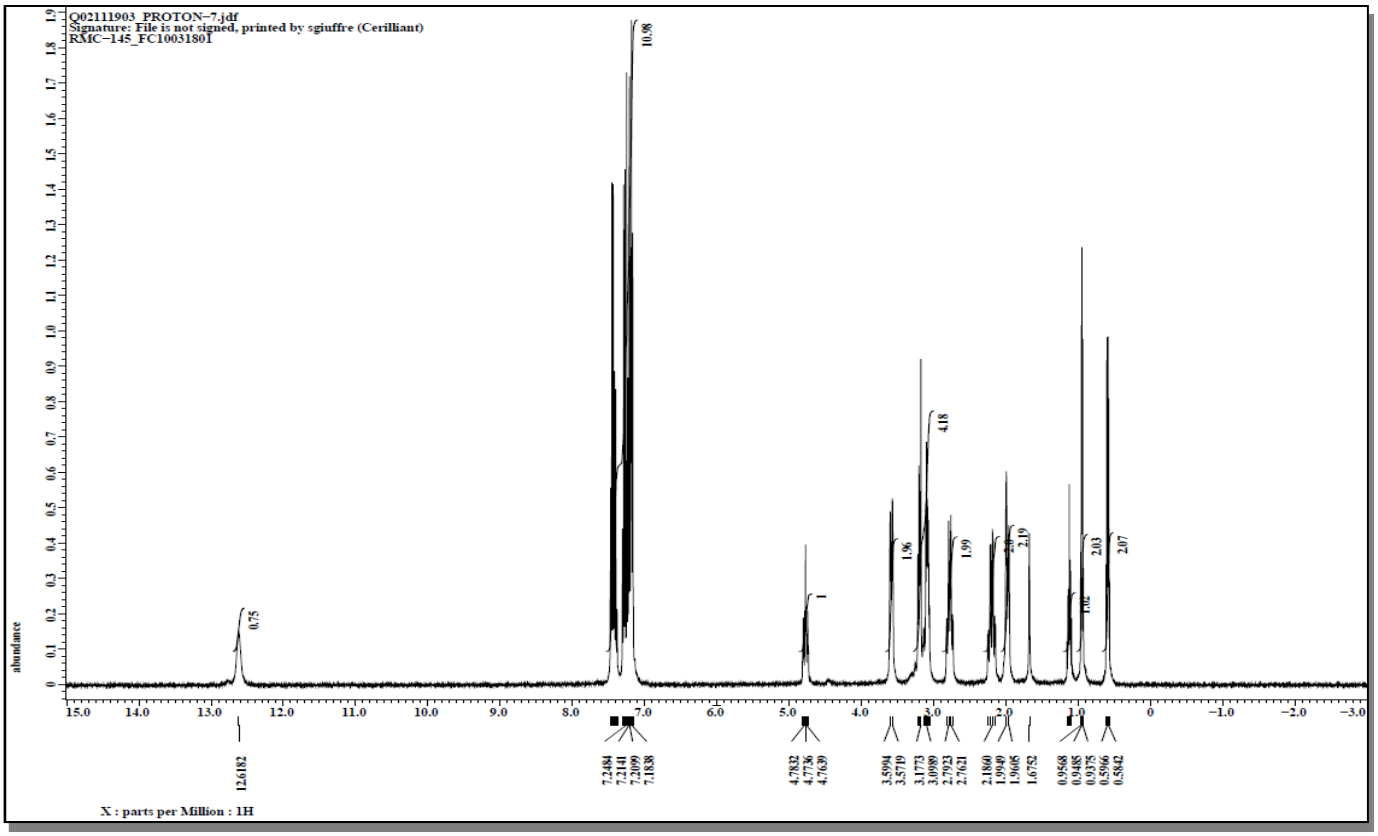
Column:	DB-ALC1 30 m x 0.53 mm, 3 µm film thickness
Temp Program:	40°C hold 12 min to 220°C at 40°C/min hold 5.5 min
Carrier Gas:	Helium
Flow Rate:	2.0 mL/min
Detector Heater Temp:	250°C
Injector:	Headspace Sampler
HS Oven Temp:	60°C
Vial Equilibration:	10 minutes
Sample Name:	FC10031801
Acquired:	February 14, 2019

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

ND - None Detected

^{1}H NMR

Instrument:	JEOL ECS 400
Solvent:	Chloroform-D



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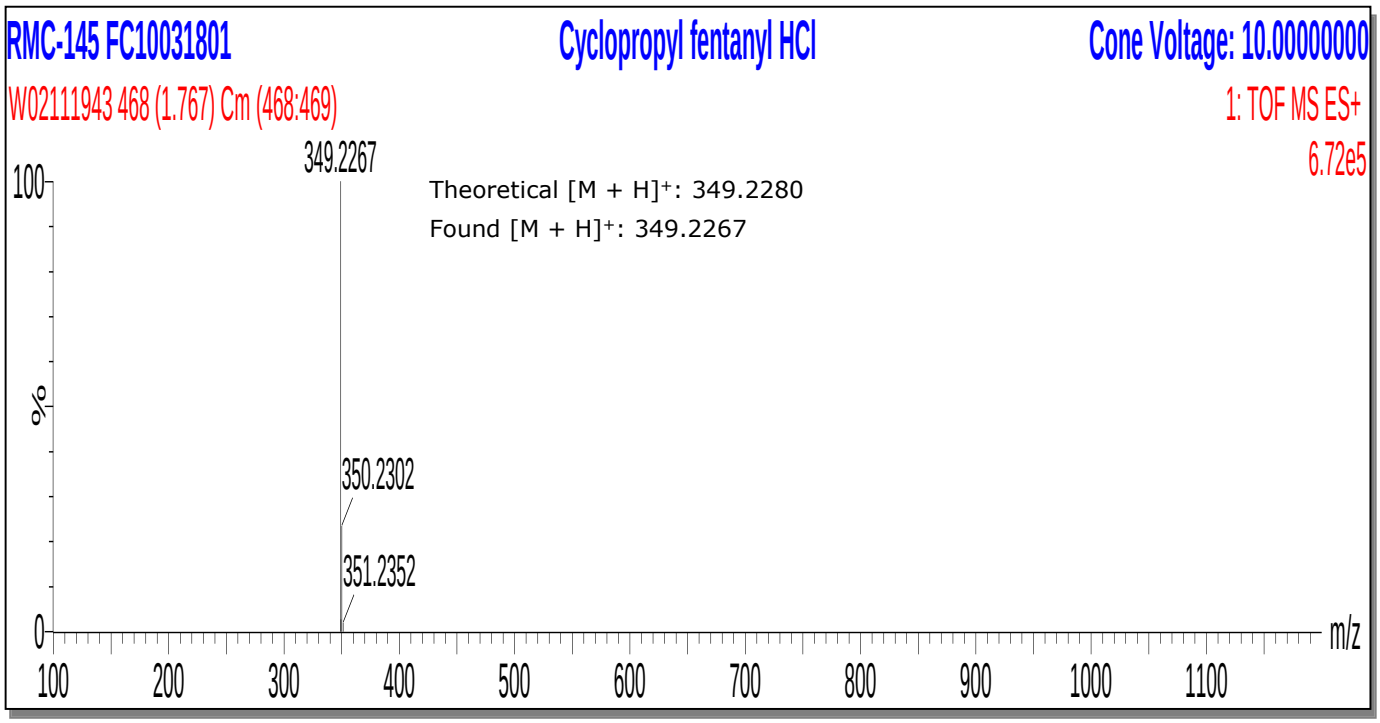
Spectral and Physical Data (cont.)

LC/MS

Column:	Ascentis Express C18, 2.7 µm, 3.0 x 50 mm	**Flow Rate:**	0.4 mL/min
Mobile Phase:	A: 0.1% Formic acid in Water B: Acetonitrile	**Scan Range:**	100-1200 amu
		Ionization:	Electrospray, Positive Ion
		Instrument:	Waters XEVO G2 QTOF
Gradient:		**Acquired:**	February 11, 2019

Time (min)	% A	% B
0.0	80	20
0.5	80	20
4.0	20	80
5.8	20	80
6.0	80	20
8.0	80	20



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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 this product is listed below.*

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

Transport/Shipping: *Stability studies support the transport of this product at ambient conditions.*

Long Term Stability: *Long term stability has been assessed for Freezer storage (-10 °C to -25 °C) conditions. Stability of a minimum of 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.

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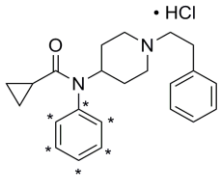
Certified Reference Material - Certificate of Analysis

Cyclopropyl fentanyl-$^{13}C_6$, Primary Measurement Standard

N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]-cyclopropanecarboxamide-$^{13}C_6$ HCl

Cerilliant Quality
ISO 17034
ISO/IEC 17025
ISO 13485
ISO 14001
ISO 9001

Product No.: C-199-1ML
Lot No.: FC12261803
Description of CRM: Cyclopropyl fentanyl-$^{13}C_6$ HCl in Methanol (Solution)
Nominal concentration is adjusted for HCl content.
Retest Date: November 2021 See Section "Stability Assessment".
Storage: Store unopened in freezer (-10 °C to -25 °C).
Shipping: Ambient. See Section "Stability Assessment".
Chemical formula: $C_{17}{}^{13}C_6H_{28}N_2O \bullet HCl$
CAS No.: NA
Regulatory: USDEA Schedule 1



Analyte	Certified Concentration ± 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 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.

Darron Ellsworth, Quality Assurance Manager

March 05, 2021
Issue Date

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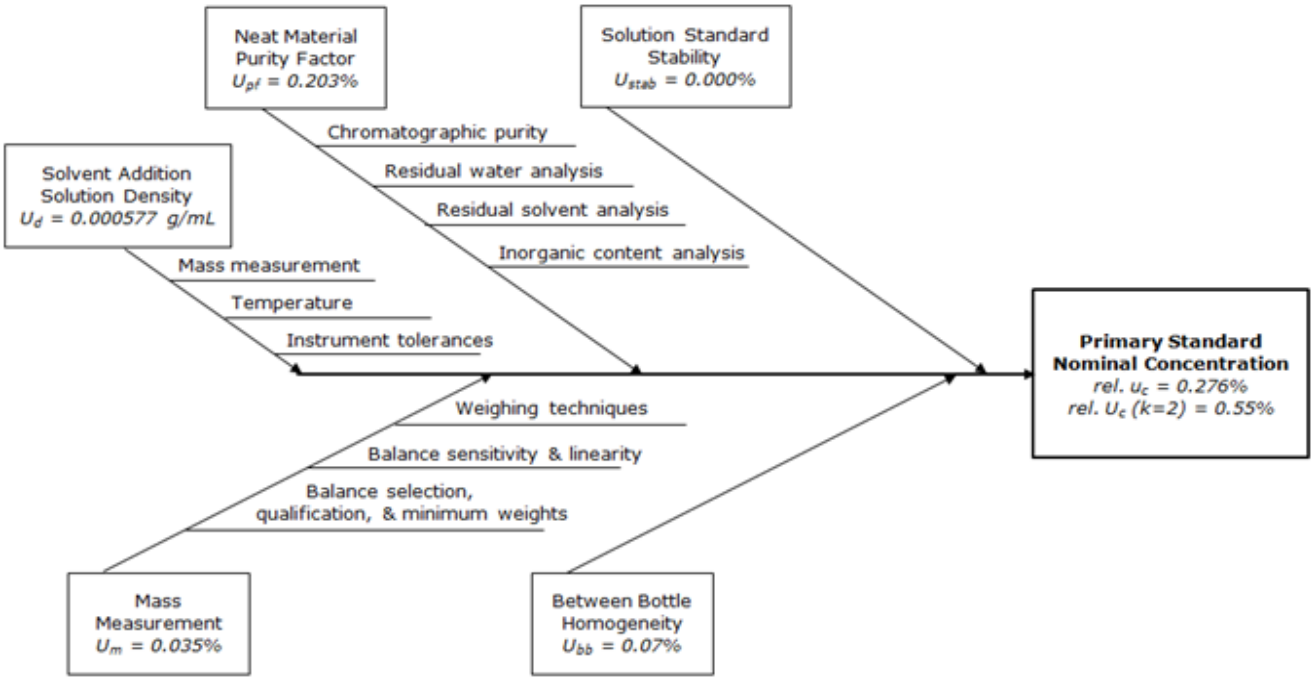
Packaging:	2 mL amber USP Type 1 glass ampoule containing not less than 1 mL of certified solution. Ampoules are overfilled to ensure a minimum of 1 mL volume can be transferred when using a 1mL Class A volumetric pipette.
Details on starting materials:	Each raw material utilized has been identified 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.



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Details on metrological traceability:

- This standard has been gravimetrically prepared using balances that have been fully qualified and calibrated to ISO 17025 requirements. All calibrations utilize NIST traceable weights which are calibrated externally by a qualified ISO 17025 accredited calibration laboratory to NIST standards. Qualification of each balance includes the assignment of a minimum weighing by a qualified and ISO 17025 accredited calibration vendor taking into consideration the balance and installed environmental conditions to ensure compliance with USP tolerances of NMT 0.10% relative error.
- Fill volume to predetermined specifications is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- The density and material Mass Balance Purity Factor of each raw material is traceable to the SI and higher order reference materials through mass measurement and instrument qualification and calibrations.

Details about certification process:

This standard has been prepared and certified under the ISO 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:	1.7 mL/min		
Wavelength:	210 nm		

		Verified Concentration (mg/mL)	**%RSD - Homogeneity**
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:	Cyclopropyl fentanyl-$^{13}C_6$ HCl	**Molecular Weight (base):**	354.44
Material Lot:	FC10031803	**Molecular Weight (salt):**	390.90
Chemical Formula:	$C_{17}{}^{13}C_6H_{28}N_2O$ • HCl	**Salt Adjustment:**	1.103
CAS Number:	NA		

Material Characterization Summary

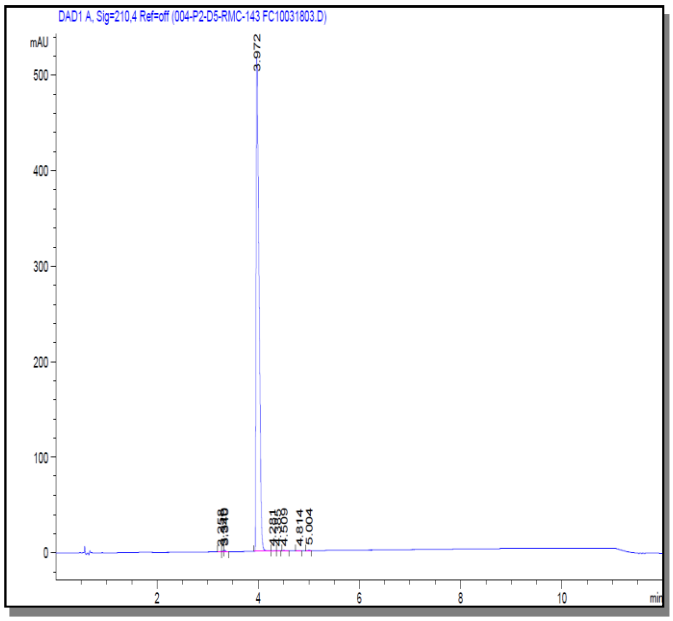
Analytical Test	**Method**	**Results**		
Primary Chromatographic Purity by HPLC/UV Analysis	SP10-0102	99.5%		
Secondary Chromatographic Purity by GC/FID Analysis	SP10-0101	99.4%		
Identity by LC/MS Analysis	SP10-0107	Consistent with Structure		
Isotopic Purity and Distribution by LC/MS SIM Analysis	SP10-0107	0.00% $^{13}C_0$ vs $^{13}C_6$		
		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>, 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]	0.55%		
Inorganic Content by Microash Analysis	SP10-0135	< 0.2%		
Elemental Analysis	Outsourced		Calculated	Analyzed
		C	52.24%	69.77%
		H	7.48%	7.44%
		N	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

HPLC/UV



Column: Ascentis Express C18, 2.7 µm, 3.0 x 100 mm

Mobile Phase: A: Acetonitrile
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/min

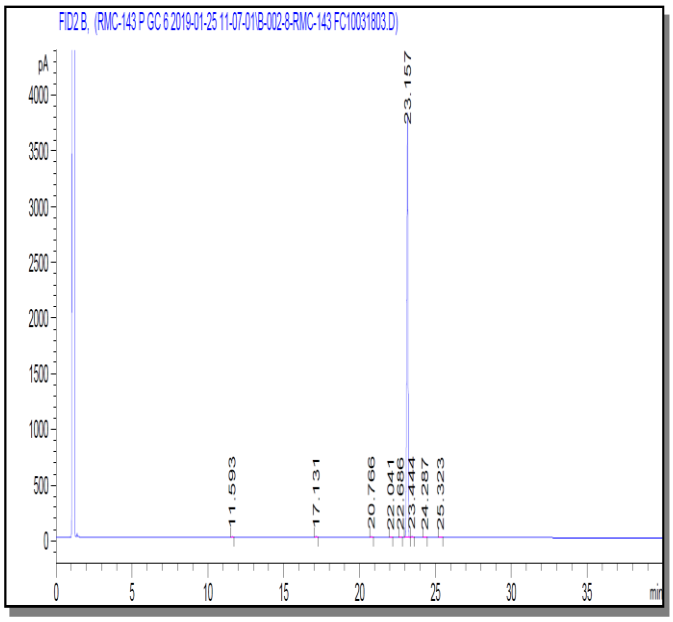
Wavelength: 210 nm

Sample Name: FC10031803

Acquired: January 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: DB-35ms, 30 m x 0.53 mm ID, 1.0 µm film thickness

Temp Program: 40°C to 200°C at 40°C/min
200°C to 300°C at 5°C/min hold 16 min

Injector Temp: Cool-on-Column

Detector Temp: 325°C

Sample Name: FC10031803

Acquired: January 25, 2019

Peak #	Ret Time	Area %
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
9	25.32	0.05

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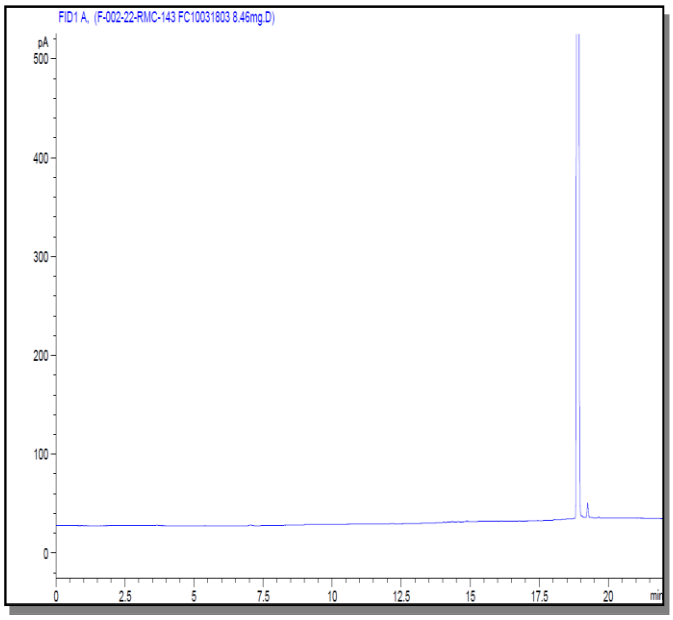
Spectral and Physical Data (cont.)

Residual Solvent Analysis by GC/FID Headspace



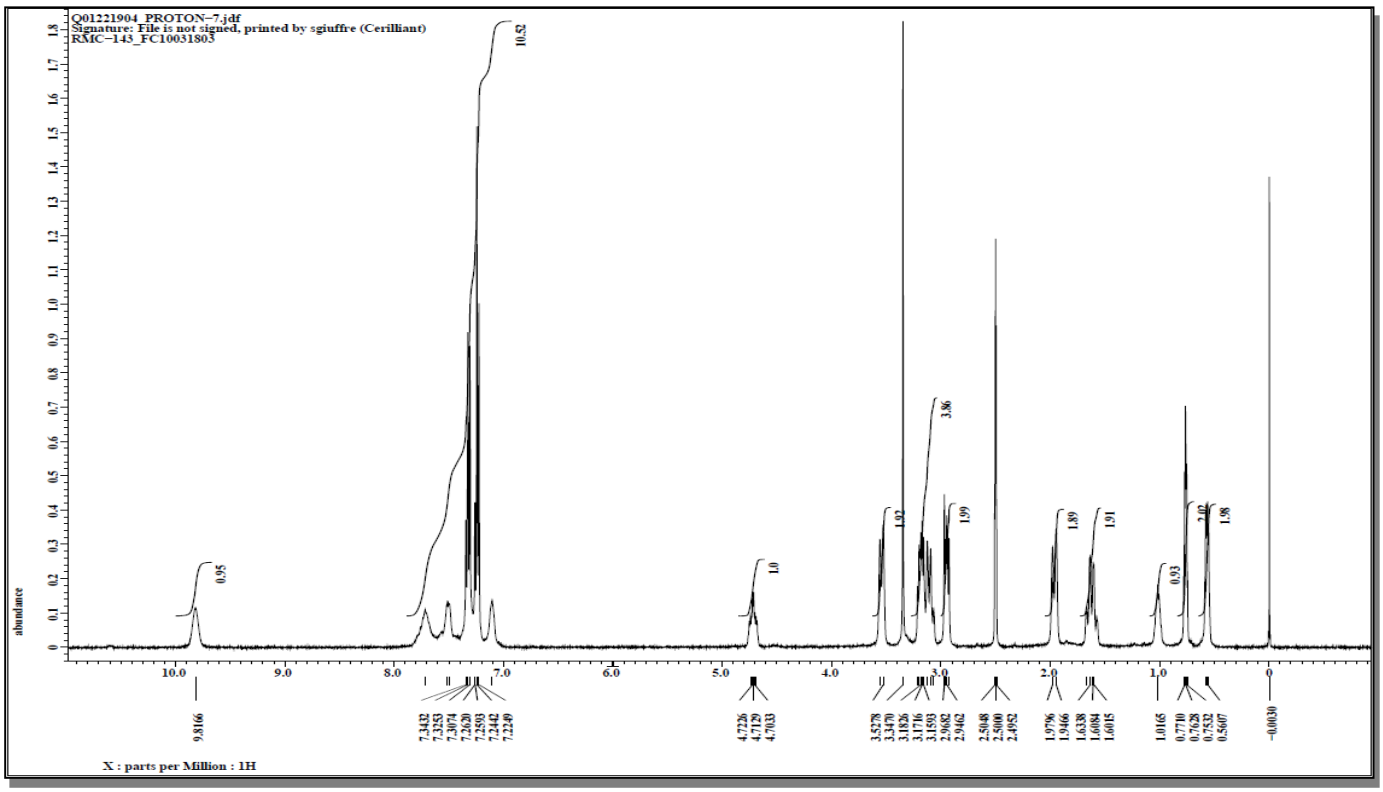
Column:	DB-ALC1 30 m x 0.53 mm, 3 µm film thickness
Temp Program:	40°C hold 12 min to 220°C at 40°C/min hold 5.5 min
Carrier Gas:	Helium
Flow Rate:	2.0 mL/min
Detector Heater Temp:	250°C
Injector:	Headspace Sampler
HS Oven Temp:	60°C
Vial Equilibration:	10 minutes
Sample Name:	FC10031803
Acquired:	January 23, 2019

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

ND - None Detected

^{1}H NMR

Instrument:	JEOL ECS 400
Solvent:	DMSO-D_6



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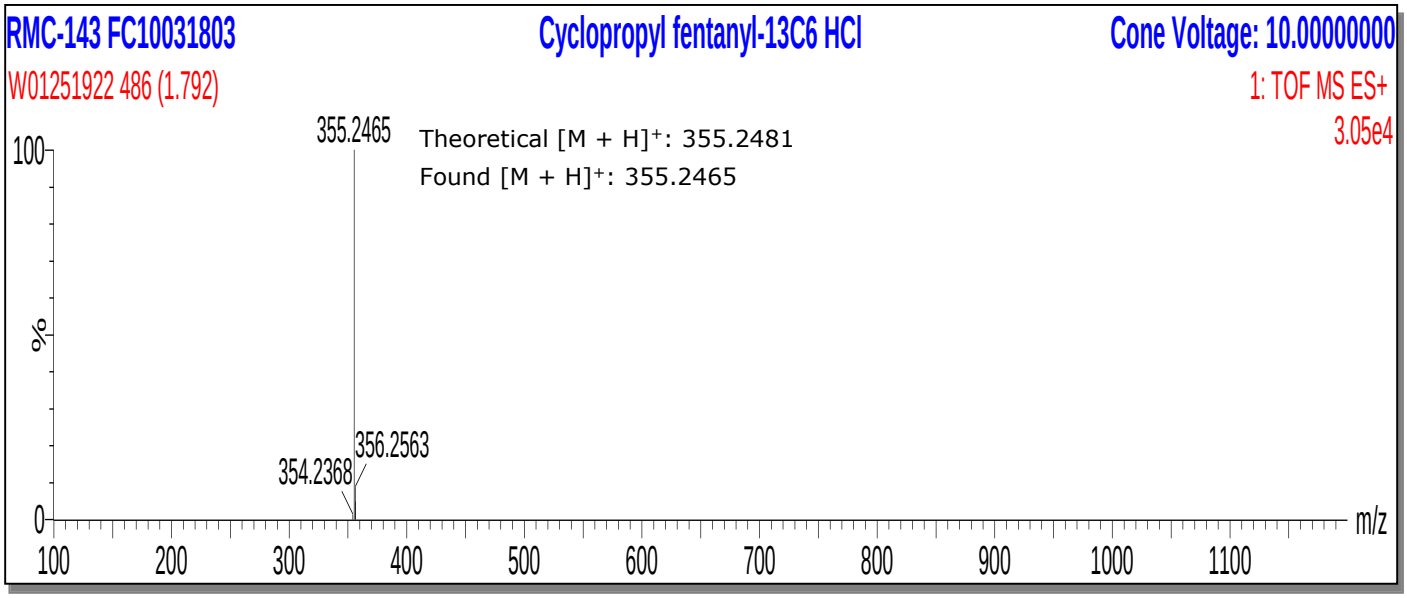
Spectral and Physical Data (cont.)

LC/MS

Column:	Ascentis Express C18, 2.7 µm, 3.0 x 50 mm	**Flow Rate:**	0.4 mL/min
Mobile Phase:	A: 0.1% Formic acid in Water B: Acetonitrile	**Scan Range:**	100-1200 amu
		Ionization:	Electrospray, Positive Ion
		Instrument:	Waters XEVO G2 QTOF
Gradient:		**Acquired:**	January 25, 2019

Time (min)	% A	% B
0.0	80	20
0.5	80	20
4.0	20	80
5.8	20	80
6.0	80	20
8.0	80	20



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Spectral and Physical Data (cont.)

Isotopic Purity by LC/MS

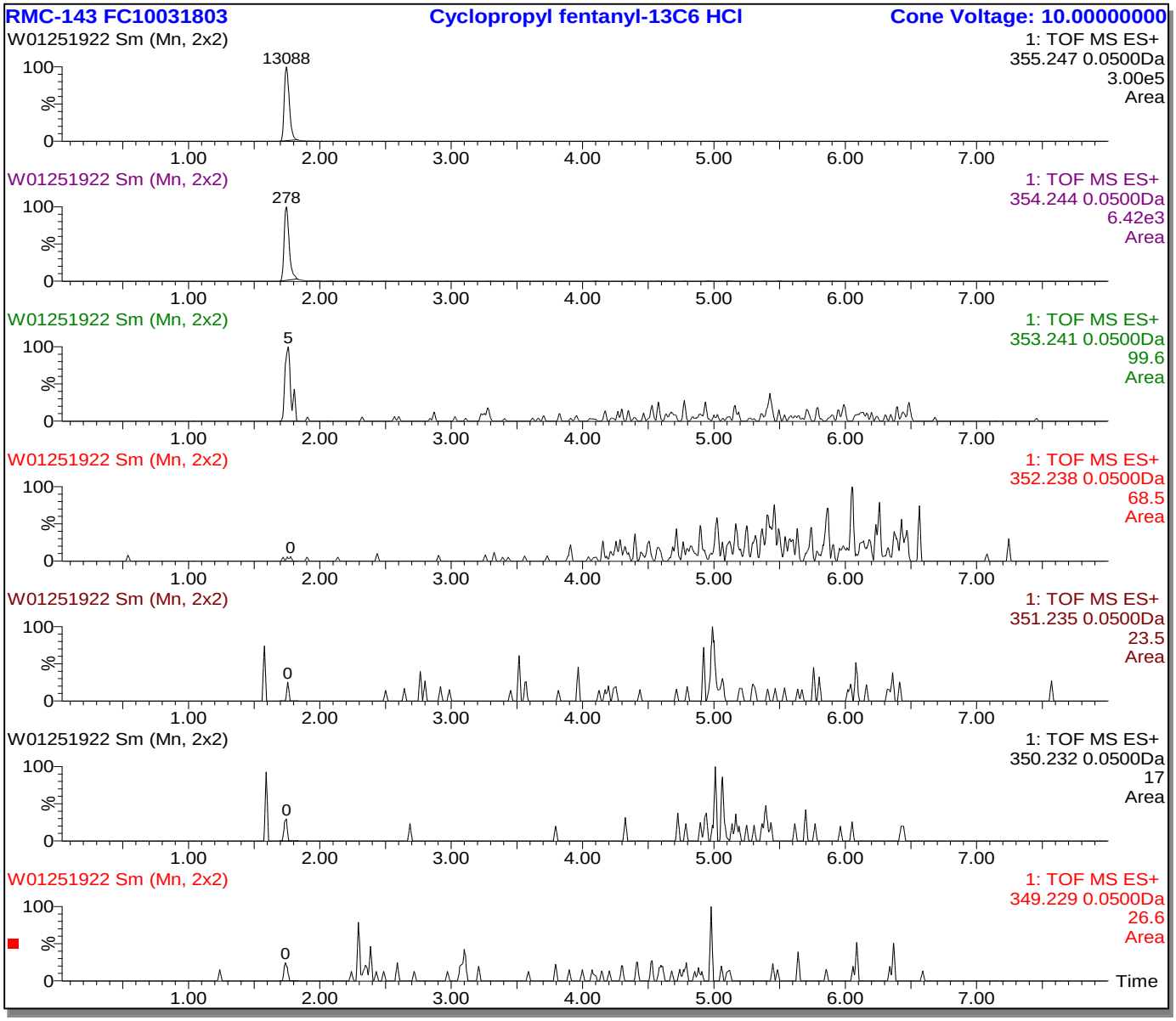
Column: Ascentis Express C18, 2.7 µm, 3.0 x 50 mm

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

Gradient:

Time (min)	% A	% B
0.0	80	20
0.5	80	20
4.0	20	80
5.8	20	80
6.0	80	20
8.0	80	20

Flow Rate: 0.4 mL/min
Scan Range: 349-355 amu
Ionization: Electrospray, Positive Ion
Instrument: Waters XEVO G2 QTOF
Acquired: January 25, 2019



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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	No decrease in purity was noted after four weeks.
Refrigerator	4°C	
Room Temperature	21°C	
40°C	40°C	

Transport/Shipping: *Stability studies support the transport of this product at ambient conditions.*

Long Term Stability: *Long term stability has been assessed for Freezer storage (-10 °C to -25 °C) conditions. Stability of a minimum of 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	April 10, 2020	Revised Retest Date from May 2020 to February 2021.
		Added Long Term Stability Section.
02	March 05, 2021	Revised Retest Date from February 2021 to November 2021.

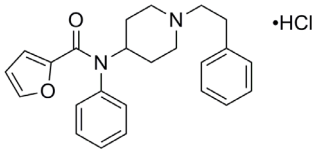
Certified Reference Material - Certificate of Analysis

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
Lot No.: FC12121801
Description of CRM: Furanyl fentanyl HCl in Methanol (Solution)
Nominal concentration is adjusted for HCl content.
Retest Date: September 2021 See Section "Stability Assessment".
Storage: Store unopened in freezer (-10 °C to -25 °C).
Shipping: Ambient. See Section "Stability Assessment".
Chemical formula: $C_{24}H_{26}N_2O_2 \bullet HCl$
CAS No.: 101365-56-4
Regulatory: USDEA Schedule I/9834

Cerilliant Quality
ISO 17034
ISO/IEC 17025
ISO 13485
ISO 14001
ISO 9001



Analyte	Certified Concentration ± associated uncertainty U, u=k*u (k=2)
Furanyl 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 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.

ANAB ACCREDITED ISO 17034 REFERENCE MATERIAL PRODUCER

Darron Ellsworth, Quality Assurance Manager

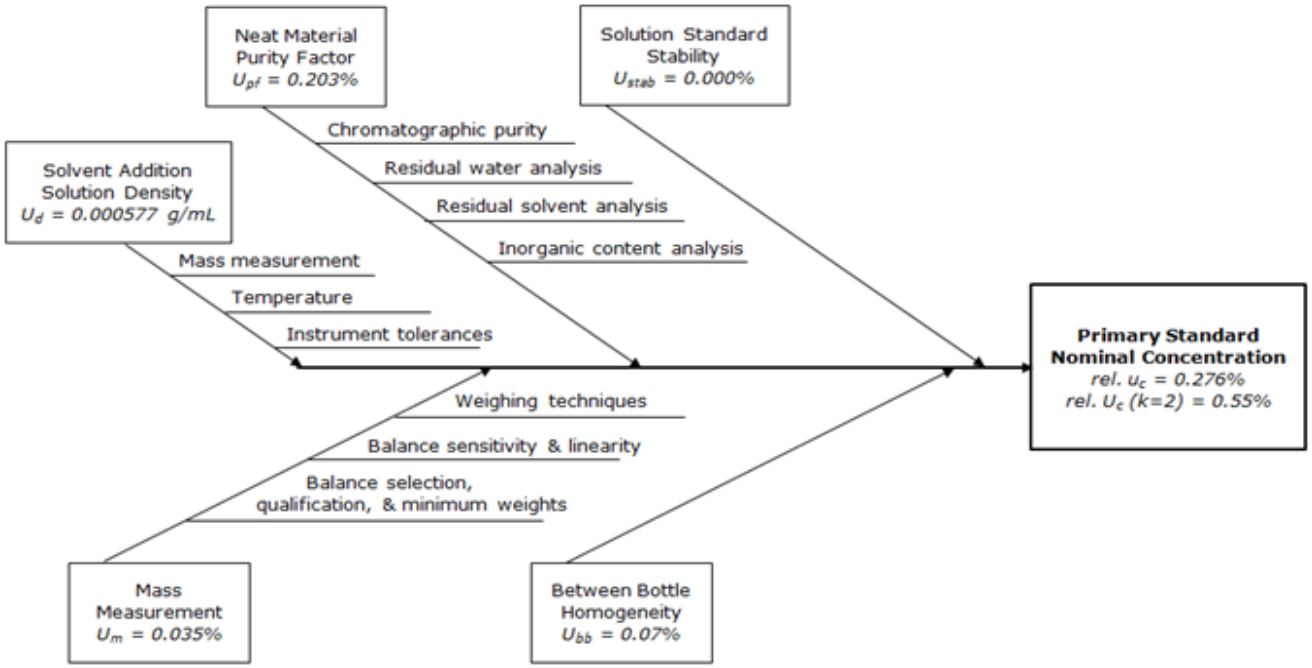
September 28, 2020
Issue Date

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.



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Details on metrological traceability:

- This standard has been gravimetrically prepared using balances that have been fully qualified and calibrated to ISO 17025 requirements. All calibrations utilize NIST traceable weights which are calibrated externally by a qualified ISO 17025 accredited calibration laboratory to NIST standards. Qualification of each balance includes the assignment of a minimum weighing by a qualified and ISO 17025 accredited calibration vendor taking into consideration the balance and installed environmental conditions to ensure compliance with USP tolerances of NMT 0.10% relative error.
- Fill volume to predetermined specifications is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- The density and material Mass Balance Purity Factor of each raw material is traceable to the SI and higher order reference materials through mass measurement and instrument qualification and calibrations.

Details about certification process:

This standard has been prepared and certified under the ISO 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 Concentration (mg/mL)	**%RSD - Homogeneity**
Standard Solution	**Lot Number**	**Actual Results**	**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.

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Analyte Certification - Mass Balance Purity Factor

Each analyte is thoroughly identified and characterized using an orthogonal approach. A mass balance purity factor is assigned incorporating chromatographic purity and residual impurities. The mass balance purity factor 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 Weight (base):**	374.48
Material Lot:	FC09271803	**Molecular Weight (salt):**	410.94
Chemical Formula:	$C_{24}H_{26}N_2O_2$•HCl	**Salt Adjustment:**	1.097
CAS Number:	101365-56-4		

Material Characterization Summary

Analytical Test	**Method**	**Results**		
Primary Chromatographic Purity by HPLC/UV Analysis	SP10-0102	99.4% [1]		
Secondary Chromatographic 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%		
Elemental Analysis	Outsourced		Calculated	Analyzed
		C	70.15%	69.48%
		H	6.62%	6.89%
		N	6.82%	7.02%
Mass Balance Purity Factor		98.11%		

[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.

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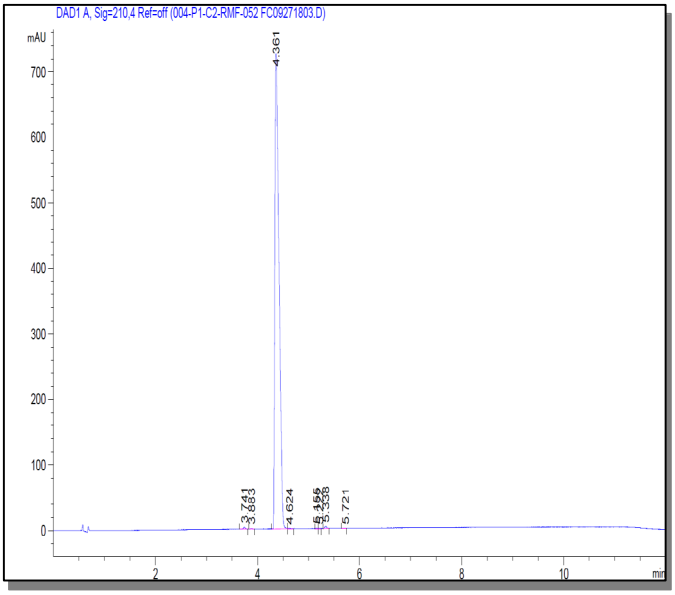
Spectral and Physical Data

HPLC/UV



Column: Ascentis Express C18, 2.7 µm, 3.0 x 100 mm

Mobile Phase: A: Acetonitrile
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/min

Wavelength: 210 nm

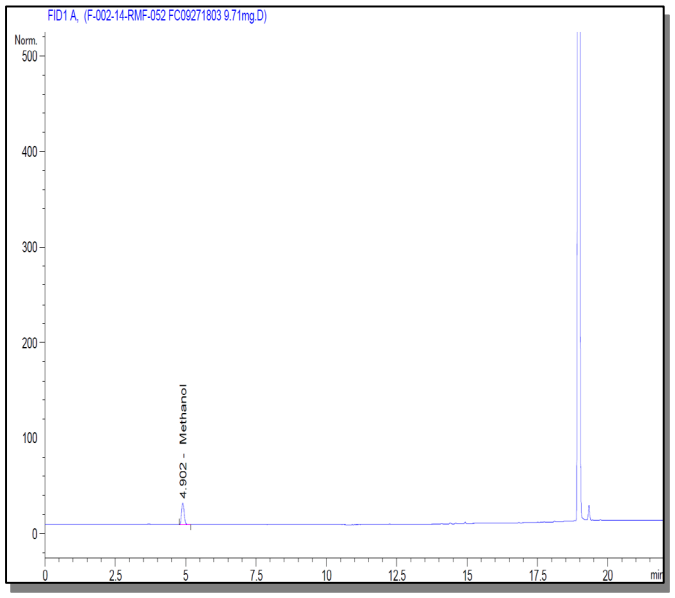
Sample Name: FC09271803

Acquired: November 12, 2018

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



Column: DB-ALC1 30 m x 0.53 mm, 3 µm film thickness

Temp Program: 40°C hold 12 min to 220°C at 40°C/min hold 5.5 min

Carrier Gas: Helium

Flow Rate: 2.0 mL/min

Detector Heater Temp: 250°C

Injector: Headspace Sampler

HS Oven Temp: 60°C

Vial Equilibration: 10 minutes

Sample Name: FC09271803

Acquired: November 14, 2018

Peak	Compound	Area	Weight %
1	Methanol	143.28	1.27
3	NMP	NA	NA
Total			**1.27**

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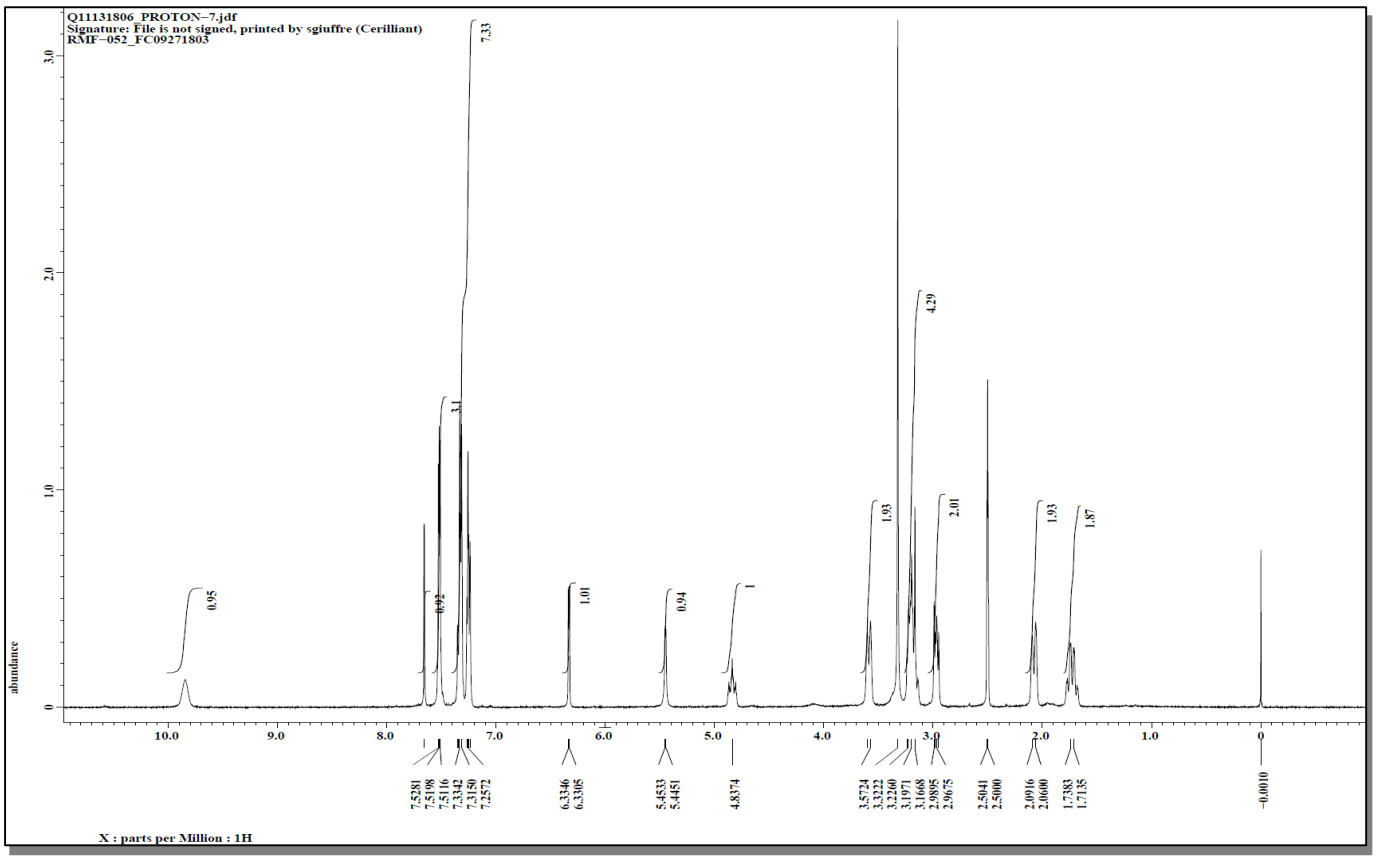
Spectral and Physical Data (cont.)

^{1}H NMR

Instrument: JEOL ECS 400
Solvent: DMSO-D_6



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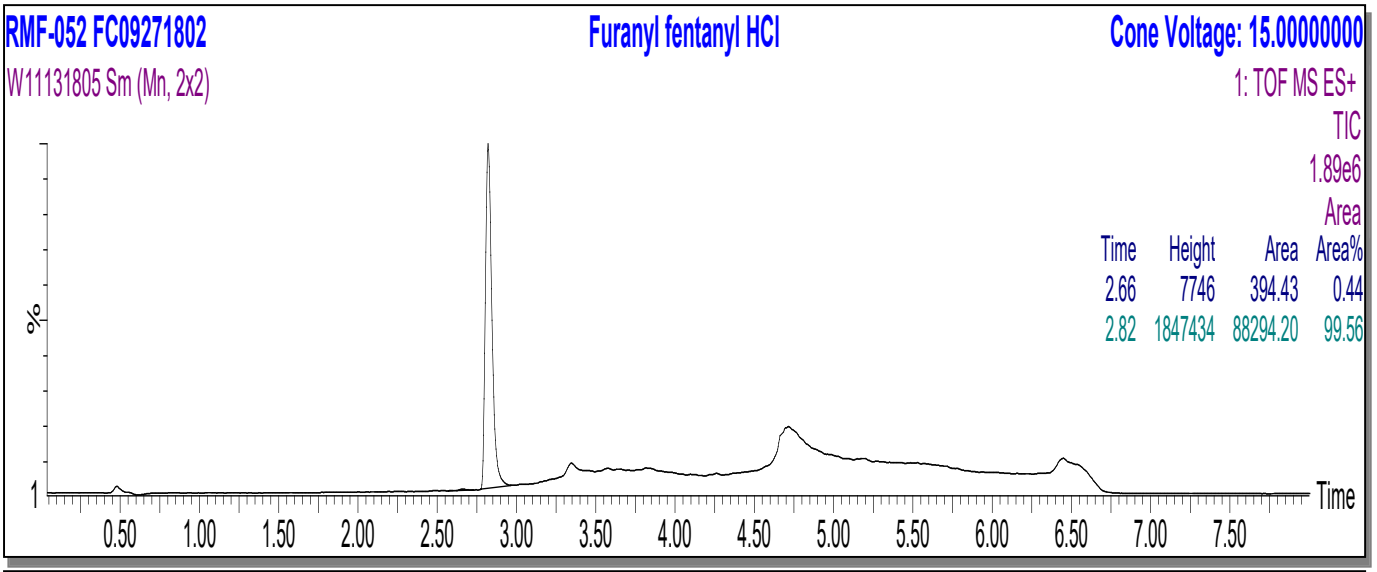
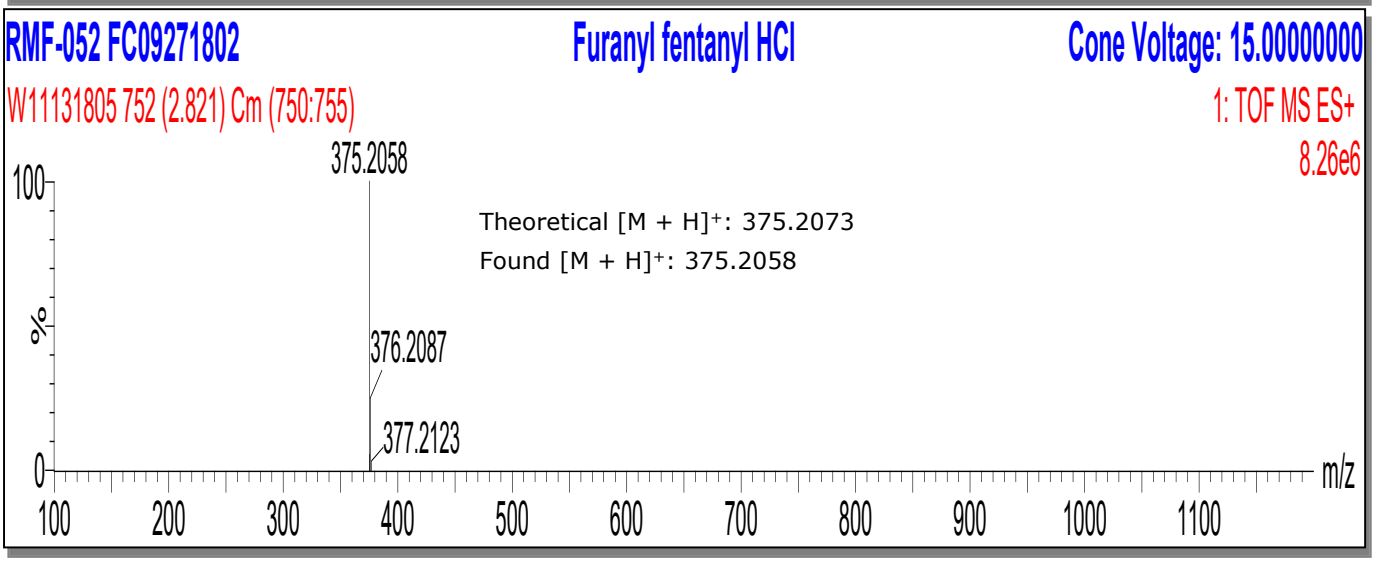
Spectral and Physical Data (cont.)

LC/MS

Column:	Ascentis Express C18, 2.7 µm, 3.0 x 50 mm	**Flow Rate:**	0.4 mL/min
Mobile Phase:	A: 0.1% Formic acid in Water B: Acetonitrile	**Scan Range:**	100-1200 amu
		Ionization:	Electrospray, Positive Ion
		Instrument:	Waters XEVO G2 QTOF
Gradient:		**Acquired:**	November 13, 2018

Time (min)	% A	% B
0.0	90	10
0.5	90	10
4.0	50	50
5.8	50	50
6.0	90	10
8.0	90	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 this product is listed below.*

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

Transport/Shipping: *Stability studies support the transport of this product at ambient conditions.*

Long Term Stability: *Long term stability has been assessed for Freezer storage (-10 °C to -25 °C) conditions. Stability of a minimum of 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	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.

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

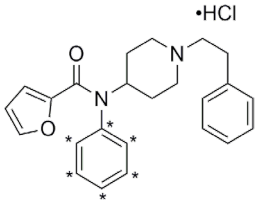
Certified Reference Material - Certificate of Analysis

Furanyl fentanyl-$^{13}C_6$, Primary Measurement Standard

N-Phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]-2-furancarboxamide-$^{13}C_6$ HCl

Cerilliant Quality
ISO 17034
ISO/IEC 17025
ISO 13485
ISO 14001
ISO 9001

Product No.: F-064-1ML
Lot No.: FC01041902
Description of CRM: Furanyl fentanyl-$^{13}C_6$ HCl in Methanol (Solution)
Nominal concentration is adjusted for HCl content.
Retest Date: September 2021 See Section "Stability Assessment".
Storage: Store unopened in freezer (-10 °C to -25 °C).
Shipping: Ambient. See Section "Stability Assessment".
Chemical formula: $C_{18}{}^{13}C_6H_{26}N_2O_2 \bullet HCl$
CAS No.: NA
Regulatory: USDEA Schedule I/9834



Analyte	Certified Concentration ± 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.

Darron Ellsworth, Quality Assurance Manager

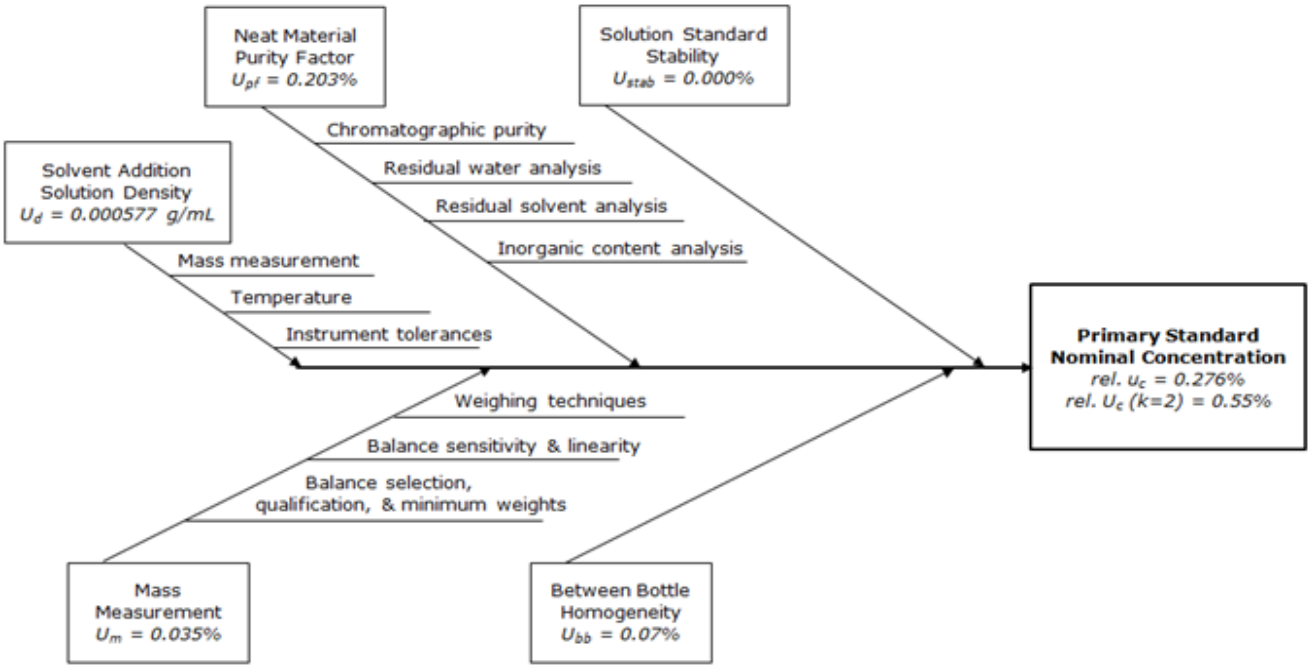
September 28, 2020
Issue Date

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.



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Details on metrological traceability:

- This standard has been gravimetrically prepared using balances that have been fully qualified and calibrated to ISO 17025 requirements. All calibrations utilize NIST traceable weights which are calibrated externally by a qualified ISO 17025 accredited calibration laboratory to NIST standards. Qualification of each balance includes the assignment of a minimum weighing by a qualified and ISO 17025 accredited calibration vendor taking into consideration the balance and installed environmental conditions to ensure compliance with USP tolerances of NMT 0.10% relative error.
- Fill volume to predetermined specifications is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- The density and material Mass Balance Purity Factor of each raw material is traceable to the SI and higher order reference materials through mass measurement and instrument qualification and calibrations.

Details about certification process:

This standard has been prepared and certified under the ISO 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.

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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 (35:65)	**Linearity (r):**	1.000
Flow Rate:	1.5 mL/min		
Wavelength:	210 nm		

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

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Analyte Certification - Mass Balance Purity Factor

Each analyte is thoroughly identified and characterized using an orthogonal approach. A mass balance purity factor is assigned incorporating chromatographic purity and residual impurities. The mass balance purity factor and salt adjustment are utilized to calculate the weighing adjustment necessary to ensure accuracy of the solution standard concentration.

Material Name:	Furanyl fentanyl-$^{13}C_6$ HCl	**Molecular Weight (base):**	380.43
Material Lot:	FC10101802	**Molecular Weight (salt):**	416.89
Chemical Formula:	$C_{18}{}^{13}C_6H_{26}N_2O_2$ • HCl	**Salt Adjustment:**	1.096
CAS Number:	NA		

Material Characterization Summary

Analytical Test	**Method**	**Results**	
Primary Chromatographic Purity by HPLC/UV Analysis	SP10-0102	99.3%	
Secondary Chromatographic Purity by GC/FID Analysis	SP10-0101	99.3%	
Identity by LC/MS Analysis	SP10-0107	Consistent with Structure	
Isotopic Purity and Distribution by LC/MS SIM Analysis	SP10-0107	0.00% $^{13}C_0$ vs $^{13}C_6$	
		0.00% $^{13}C_0$	0.04% $^{13}C_4$
		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 Analysis	USP <761>, SP10-0116	Consistent with Structure	
Residual Solvent Analysis by GC/FID Headspace	AM1087 [1]	0.77%	
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		98.49%	

[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.

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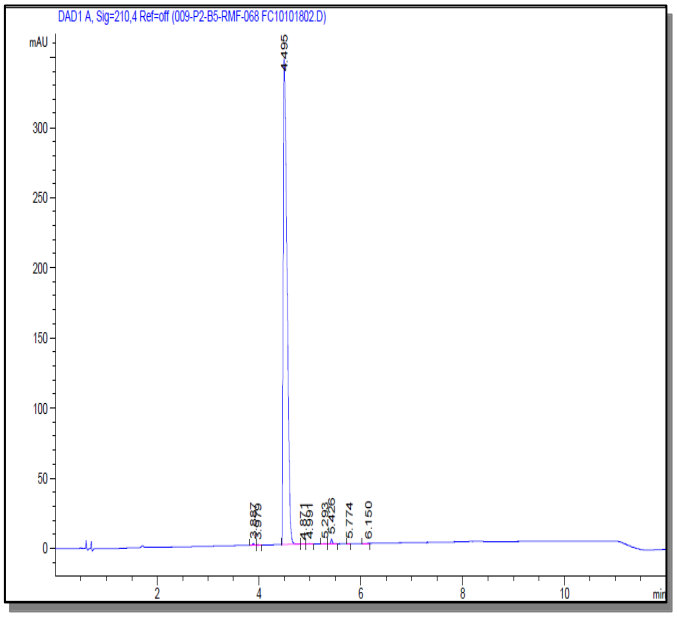
Spectral and Physical Data

HPLC/UV



Column: Ascentis Express Phenyl-Hexyl, 2.7 µm, 3.0 x 100 mm

Mobile Phase: A: Acetonitrile
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/min

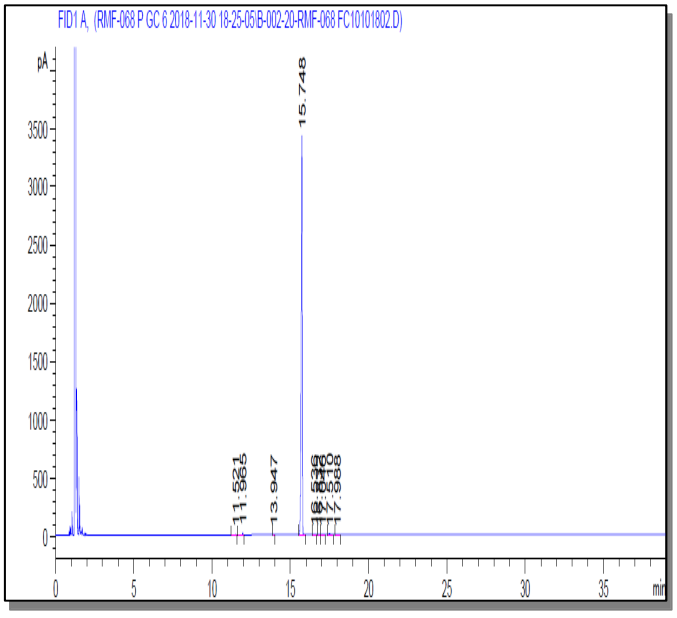
Wavelength: 210 nm

Sample Name: FC10101802

Acquired: December 04, 2018

Peak #	Ret Time	Area %
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
9	6.15	0.01

GC/FID



Column: DB-5ms, 30 m x 0.53 mm ID, 1.5 µm film thickness

Temp Program: 60°C to 300°C at 20°C/min hold 27 min

Injector Temp: Cool-on-Column

Detector Temp: 325°C

Sample Name: FC10101802

Acquired: November 30, 2018

Peak #	Ret Time	Area %
1	11.52	0.05
2	11.97	0.16
3	13.95	0.00
4	15.75	99.27
5	16.54	0.04
6	16.83	0.01
7	17.05	0.06
8	17.51	0.40
9	17.99	0.01

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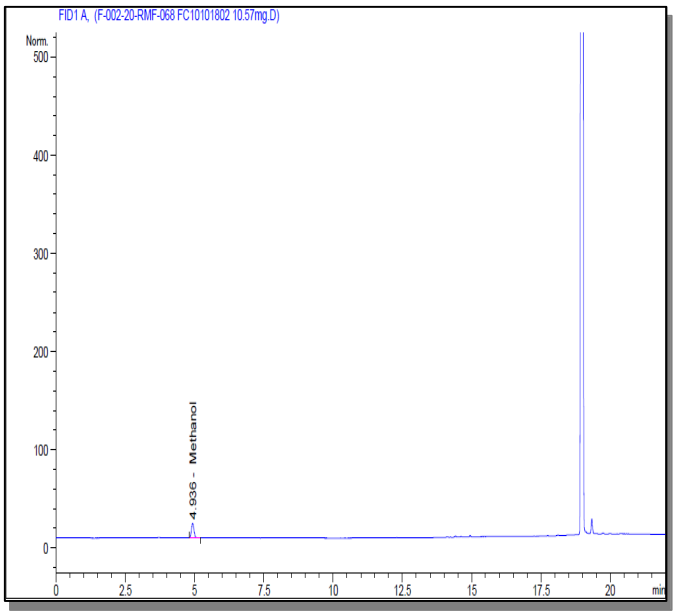
Spectral and Physical Data (cont.)

Residual Solvent Analysis by GC/FID Headspace

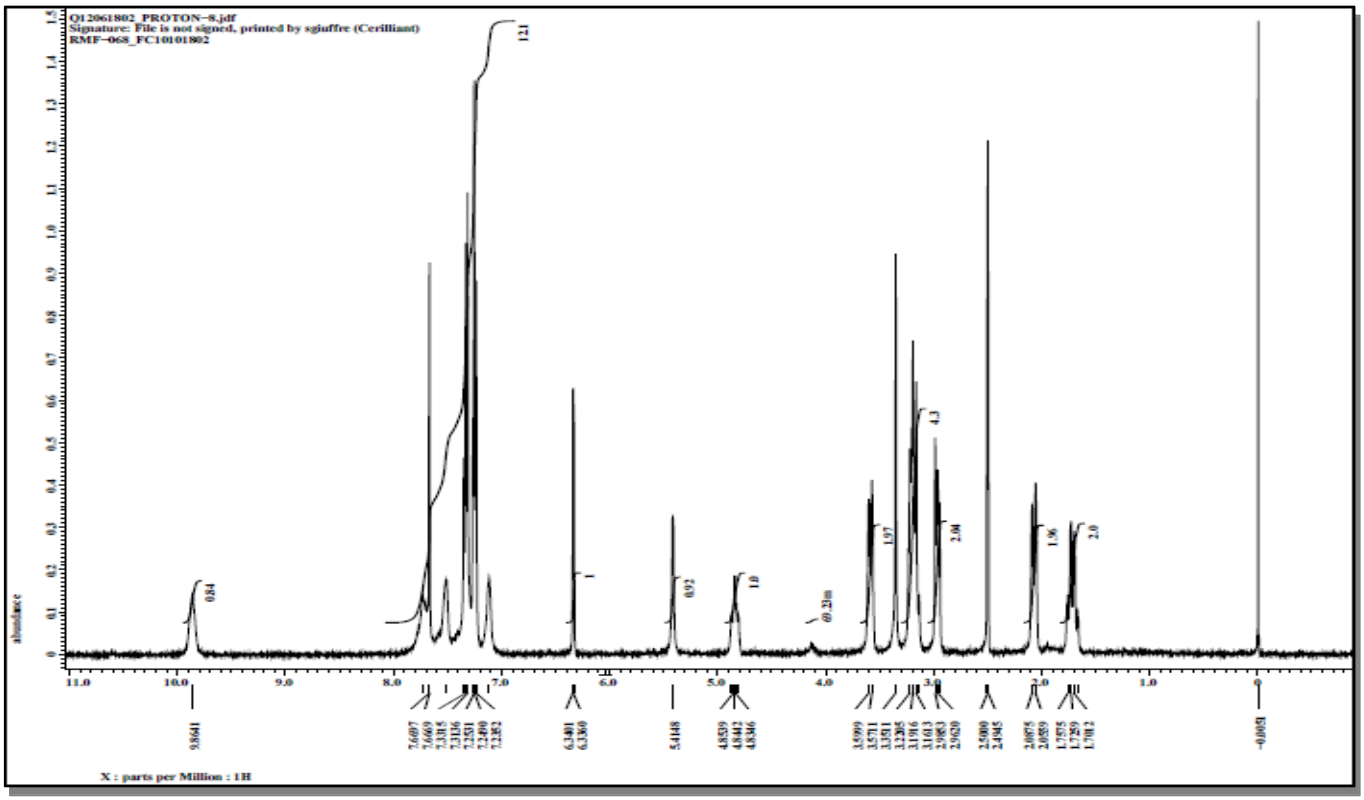


Column:	DB-ALC1 30 m x 0.53 mm, 3 µm film thickness
Temp Program:	40°C hold 12 min to 220°C at 40°C/min hold 5.5 min
Carrier Gas:	Helium
Flow Rate:	2.0 mL/min
Detector Heater Temp:	250°C
Injector:	Headspace Sampler
HS Oven Temp:	60°C
Vial Equilibration:	10 minutes
Sample Name:	FC10101802
Acquired:	December 06, 2018

Peak	Compound	Area	Weight %
1	Methanol	94.72	0.77
2	NMP	NA	NA
Total			**0.77**

^{1}H NMR

Instrument: JEOL ECS 400
Solvent: DMSO-D_6



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Spectral and Physical Data (cont.)

LC/MS

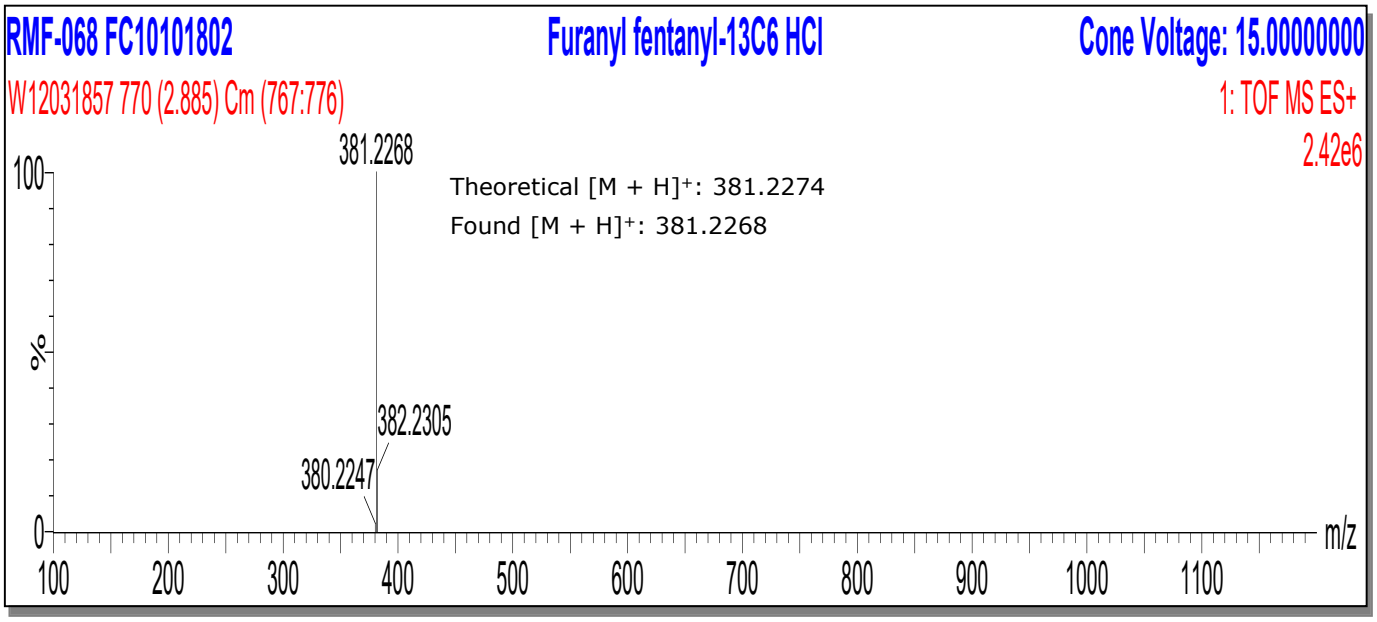
Column: Ascentis Express C18, 2.7 µm, 3.0 x 50 mm
Mobile Phase: A: 0.1% Formic acid in Water
B: Acetonitrile

Gradient:

Time (min)	% A	% B
0.0	90	10
0.5	90	10
4.0	50	50
5.8	50	50
6.0	90	10
8.0	90	10

Flow Rate: 0.4 mL/min
Scan Range: 100-1200 amu
Ionization: Electrospray, Positive Ion

Instrument: Waters XEVO G2 QTOF
Acquired: December 03, 2018



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Spectral and Physical Data (cont.)

Isotopic Purity by LC/MS SIM

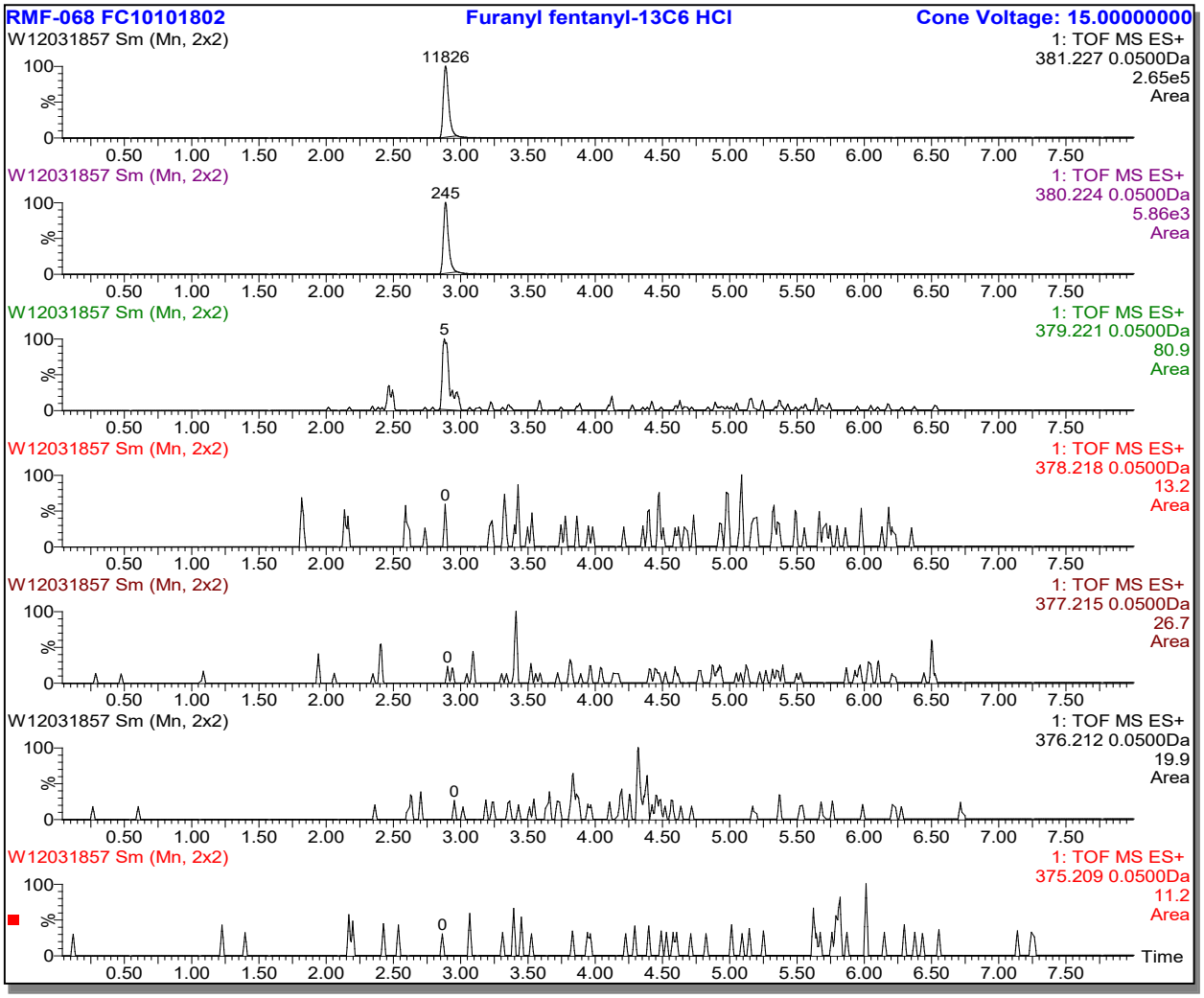
Column: Ascentis Express C18, 2.7 µm, 3.0 x 50 mm
Mobile Phase: A: 0.1% Formic acid in Water
B: Acetonitrile

Gradient:

Time (min)	% A	% B
0.0	90	10
0.5	90	10
4.0	50	50
5.8	50	50
6.0	90	10
8.0	90	10

Flow Rate: 0.4 mL/min
Scan Range: 375-381 amu
Ionization: Electrospray, Positive Ion

Instrument: Waters XEVO G2 QTOF
Acquired: December 03, 2018



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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 (F-046-0.5ML, Furanyl fentanyl HCl) is listed below.*

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

Transport/Shipping: *Stability studies support the transport of this product at ambient conditions.*

Long Term Stability: *Long term stability has been assessed for Freezer storage (-10 °C to -25 °C) conditions. Stability of a minimum of 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.

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

Certified Reference Material - Certificate of Analysis

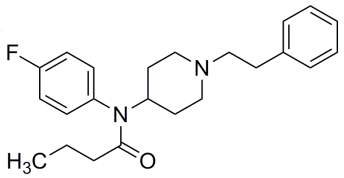
para-Fluorobutyryl fentanyl, Primary Measurement Standard

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

4-Fluorobutyryl fentanyl (4-FBF, 4F-BF); para-Fluorobutyryl fentanyl (p-FBF); p-Fluorobutyryl fentanyl (p-FBF)

Cerilliant Quality
ISO 17034
ISO/IEC 17025
ISO 13485
ISO 14001
ISO 9001

Product No.: F-065-1ML
Lot No.: FC01071902
Description of CRM: para-Fluorobutyryl fentanyl in Methanol (Solution)
Retest Date: January 2022 See Section "Stability Assessment".
Storage: Store unopened in freezer (-10 °C to -25 °C).
Shipping: Ambient. See Section "Stability Assessment"
Chemical formula: $C_{23}H_{29}FN_2O$
CAS No.: 244195-31-1
Regulatory: USDEA Schedule I



Analyte	Certified Concentration ± 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 µL for quantitative applications

Instructions for handling and correct use: Concentration is corrected for chromatographic purity, residual water, residual solvents and residual inorganics. No adjustment required before use.
Users should quantitatively transfer desired volume using established good laboratory practices to spike into matrix or to dilute to the desired concentration. Each ampoule is intended for one-time use.

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

Accreditation: Cerilliant Corp. is accredited by the US accreditation authority ANAB as registered reference material producer AR-1353 in accordance with ISO 17034 and registered testing laboratory AT-1352 according to ISO/IEC 17025.

ANAB ACCREDITED ISO 17034 REFERENCE MATERIAL PRODUCER

Darron Ellsworth, Quality Assurance Manager

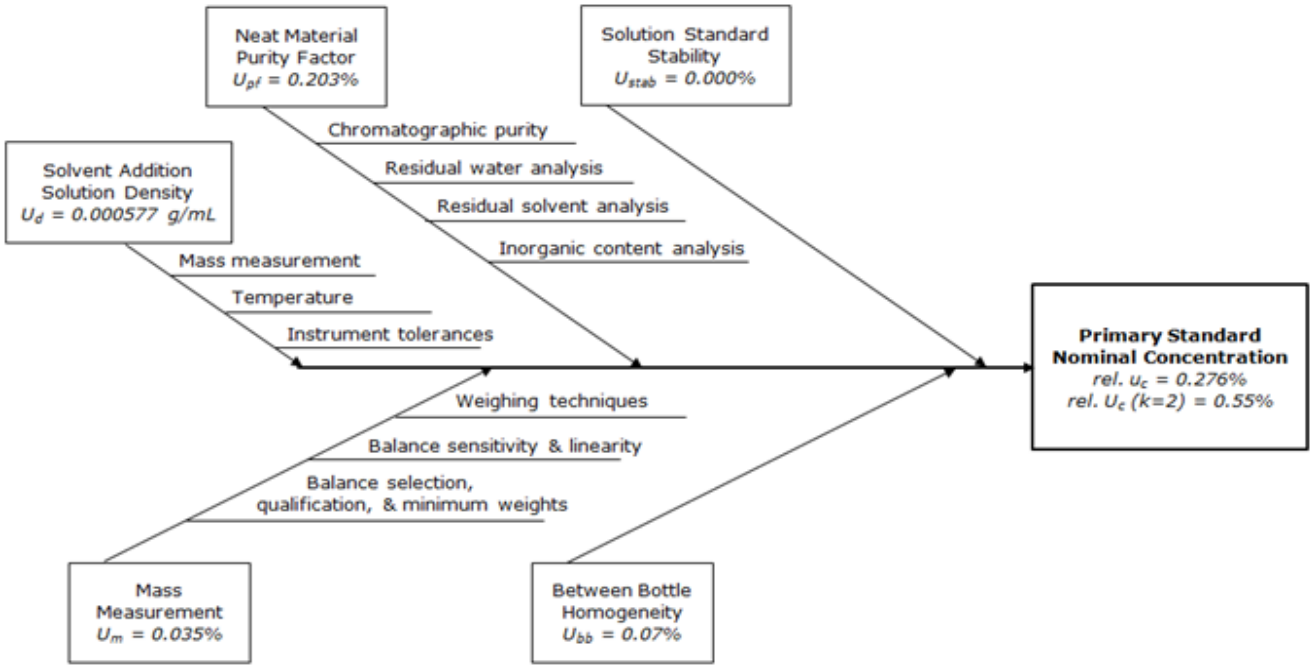
February 02, 2021
Issue Date

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.



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Details on metrological traceability:

- This standard has been gravimetrically prepared using balances that have been fully qualified and calibrated to ISO 17025 requirements. All calibrations utilize NIST traceable weights which are calibrated externally by a qualified ISO 17025 accredited calibration laboratory to NIST standards. Qualification of each balance includes the assignment of a minimum weighing by a qualified and ISO 17025 accredited calibration vendor taking into consideration the balance and installed environmental conditions to ensure compliance with USP tolerances of NMT 0.10% relative error.
- Fill volume to predetermined specifications is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- The density and material Mass Balance Purity Factor of each raw material is traceable to the SI and higher order reference materials through mass measurement and instrument qualification and calibrations.

Details about certification process:

This standard has been prepared and certified under the ISO 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 (mg/mL)	**%RSD - 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.

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Analyte Certification - Mass Balance Purity Factor

Each analyte is thoroughly identified and characterized using an orthogonal approach. A mass balance purity factor is assigned incorporating chromatographic purity and residual impurities. The mass balance purity factor is utilized to calculate the weighing adjustment necessary to ensure accuracy of the solution standard concentration.

Material Name:	para-Fluorobutyryl fentanyl	**Chemical Formula:**	$C_{23}H_{29}FN_2O$
Material Lot:	FC09241801	**CAS Number:**	244195-31-1
		Molecular Weight:	368.49

Material Characterization Summary

Analytical Test	**Method**	**Results**		
Primary Chromatographic Purity by HPLC/UV Analysis	SP10-0102	99.7% [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]	None Detected		
Residual Water Analysis by Karl Fischer Coulometry	AM1346 [2]	Not Detected		
Elemental Analysis	Outsourced		Calculated	Analyzed
		C	74.97%	75.25%
		H	7.93%	7.90%
		N	7.60%	7.82%
Mass Balance Purity Factor		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.

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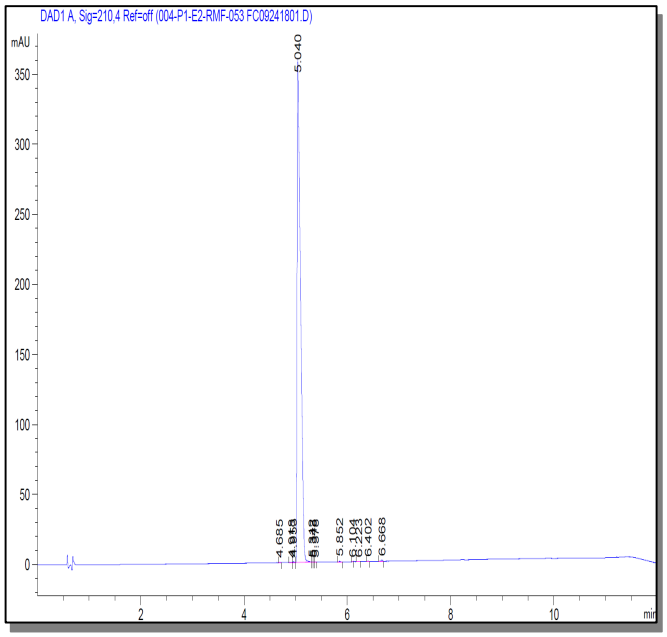
Spectral and Physical Data

HPLC/UV



Column: Ascentis Express C18, 2.7 µm, 3.0 x 100 mm

Mobile Phase: A: Acetonitrile
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/min

Wavelength: 210 nm

Sample Name: FC09241801

Acquired: February 25, 2019

Peak #	Ret Time	Area %
1	4.69	0.01
2	4.92	0.02
3	4.95	0.06
4	5.04	99.65
5	5.31	0.02
6	5.34	0.01
7	5.38	0.01
8	5.85	0.05
9	6.10	0.01
10	6.22	0.03
11	6.40	0.03
12	6.67	0.11

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

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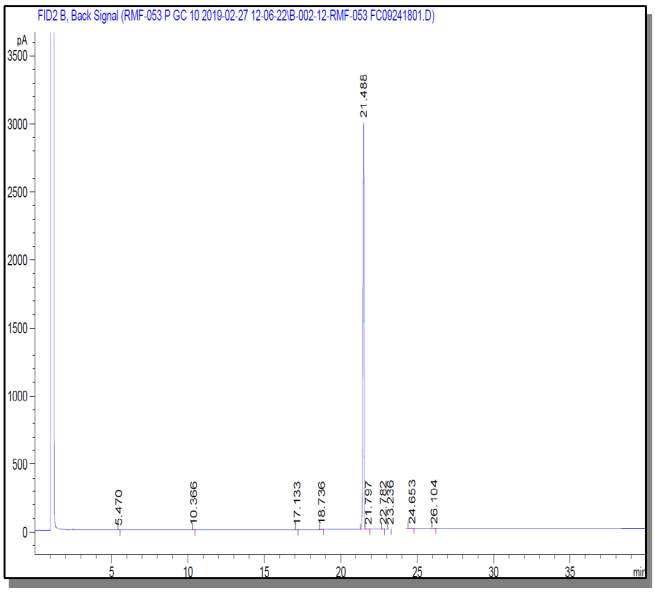
Spectral and Physical Data (cont.)

GC/FID

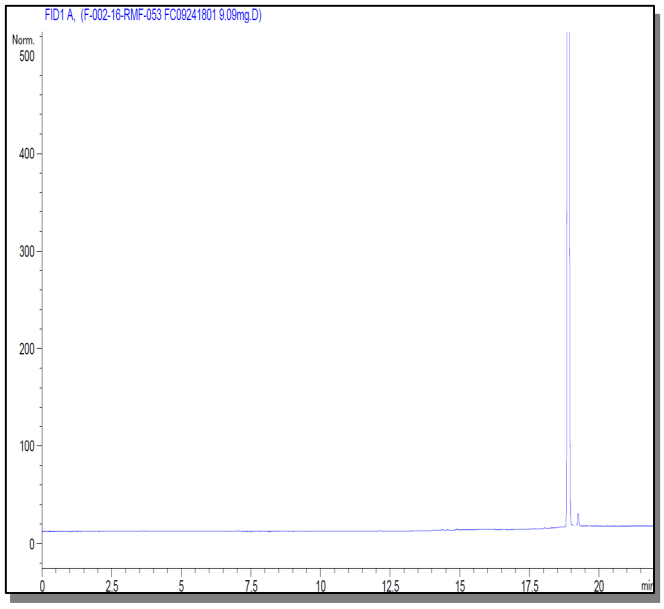


Column: DB-35ms, 30 m x 0.53 mm ID, 1.0 µm film thickness
Temp Program: 40°C to 200°C at 40°C/min
200°C to 300°C at 5°C/min
hold 16 min
Injector Temp: Cool-on-Column
Detector Temp: 325°C

Sample Name: FC09241801
Acquired: February 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
7	22.78	0.01
8	23.24	0.03
9	24.65	0.05
10	26.10	0.03

Residual Solvent Analysis by GC/FID Headspace



Column: DB-ALC1 30 m x 0.53 mm, 3 µm film thickness
Temp Program: 40°C hold 12 min to 220°C at 40°C/min hold 5.5 min
Carrier Gas: Helium
Flow Rate: 2.0 mL/min
Detector Heater Temp: 250°C
Injector: Headspace Sampler
HS Oven Temp: 60°C
Vial Equilibration: 10 minutes

Sample Name: FC09241801
Acquired: February 26, 2019

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

ND - None Detected

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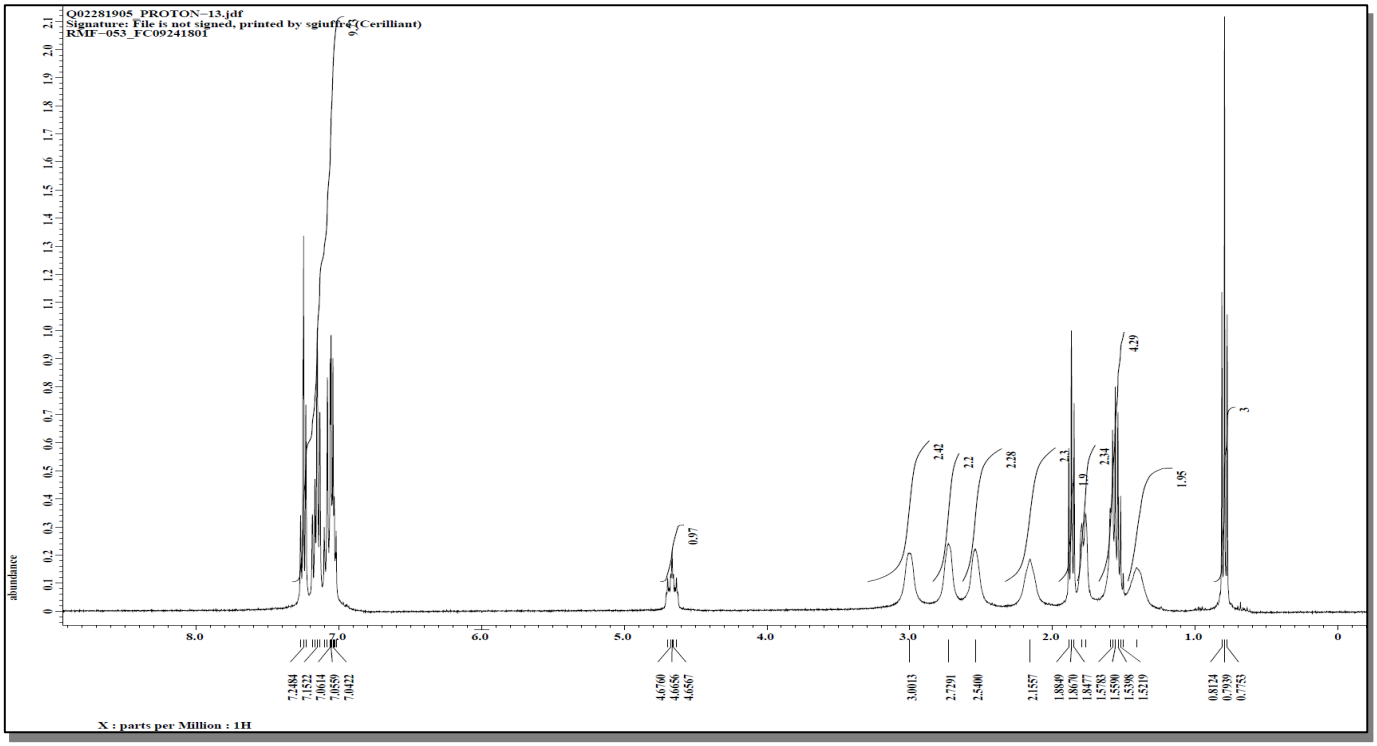
Spectral and Physical Data (cont.)

^{1}H NMR

Instrument: JEOL ECS 400
Solvent: Chloroform-D



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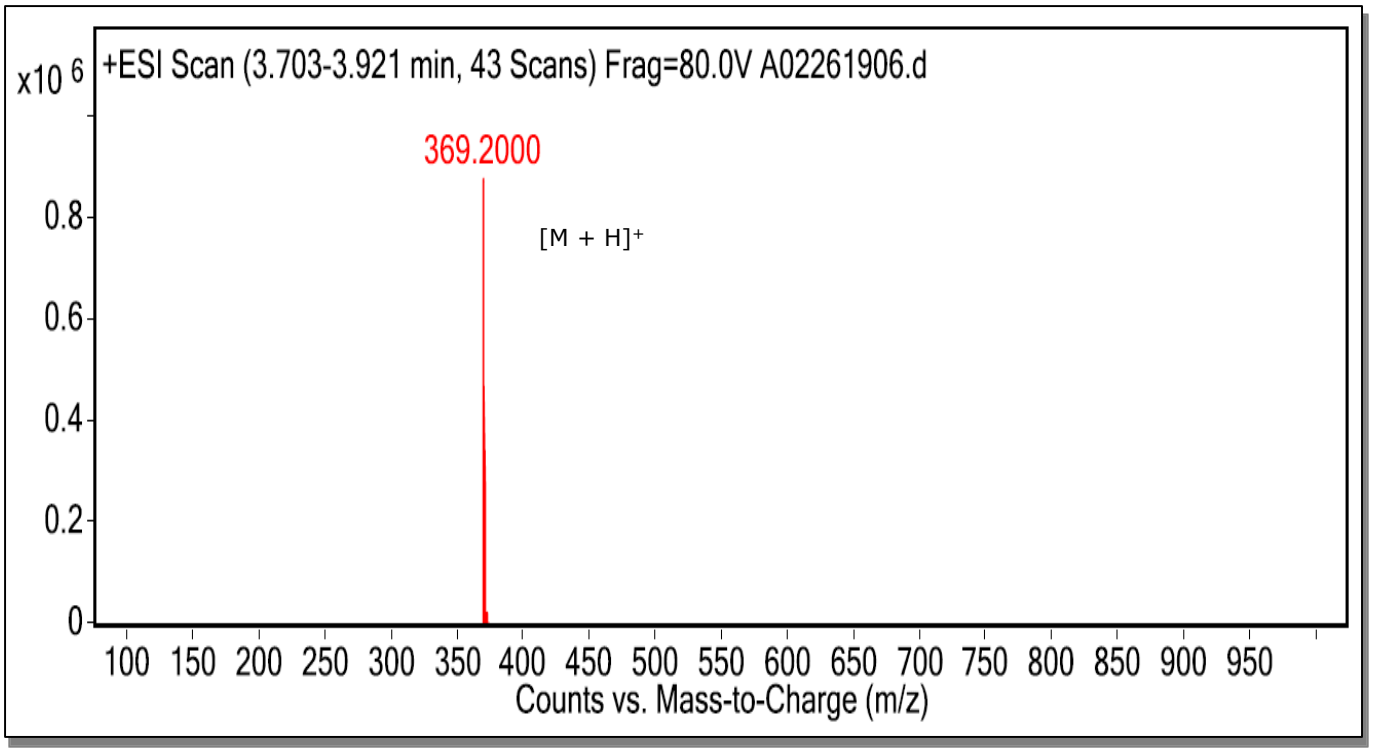
Spectral and Physical Data (cont.)

LC/MS

Column:	Kinetex C18, 2.6 µm, 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: Acetonitrile			**Ionization:**	Electrospray, Positive Ion
Gradient:	Time (min)	% A	% B	**Instrument:**	Agilent 6410A Mass Spectrometer
	0.0	80	20	**Acquired:**	February 26, 2019
	5.0	20	80		
	6.0	20	80		
	7.0	80	20		
	11.0	80	20		



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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 this product is listed below.*

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

Transport/Shipping: *Stability studies support the transport of this product at ambient conditions.*

Long Term Stability: *Long term stability has been assessed for Freezer storage (-10 °C to -25 °C) conditions. Stability of a minimum of 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.

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

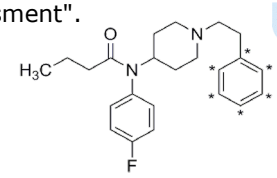
Certified Reference Material - Certificate of Analysis

para-Fluorobutyryl fentanyl-$^{13}C_6$, Primary Measurement Standard

N-(4-Fluorophenyl)-N-(1-phenethylpiperidin-4-yl)butyramide-$^{13}C_6$

Cerilliant Quality
ISO 17034
ISO/IEC 17025
ISO 13485
ISO 14001
ISO 9001

Product No.: F-066-1ML
Lot No.: FC01031902
Description of CRM: para-Fluorobutyryl fentanyl-$^{13}C_6$ in Methanol (Solution)
Retest Date: November 2021 See Section "Stability Assessment".
Storage: Store unopened in freezer (-10 °C to -25 °C).
Shipping: Ambient. See Section "Stability Assessment".
Chemical formula: $C_{17}{}^{13}C_6H_{29}N_2OF$
CAS No.: NA
Regulatory: USDEA Schedule I



Analyte	Certified Concentration ± associated uncertainty U, u=k*u (k=2)
para-Fluorobutyryl 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.
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

December 09, 2020
Issue Date

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

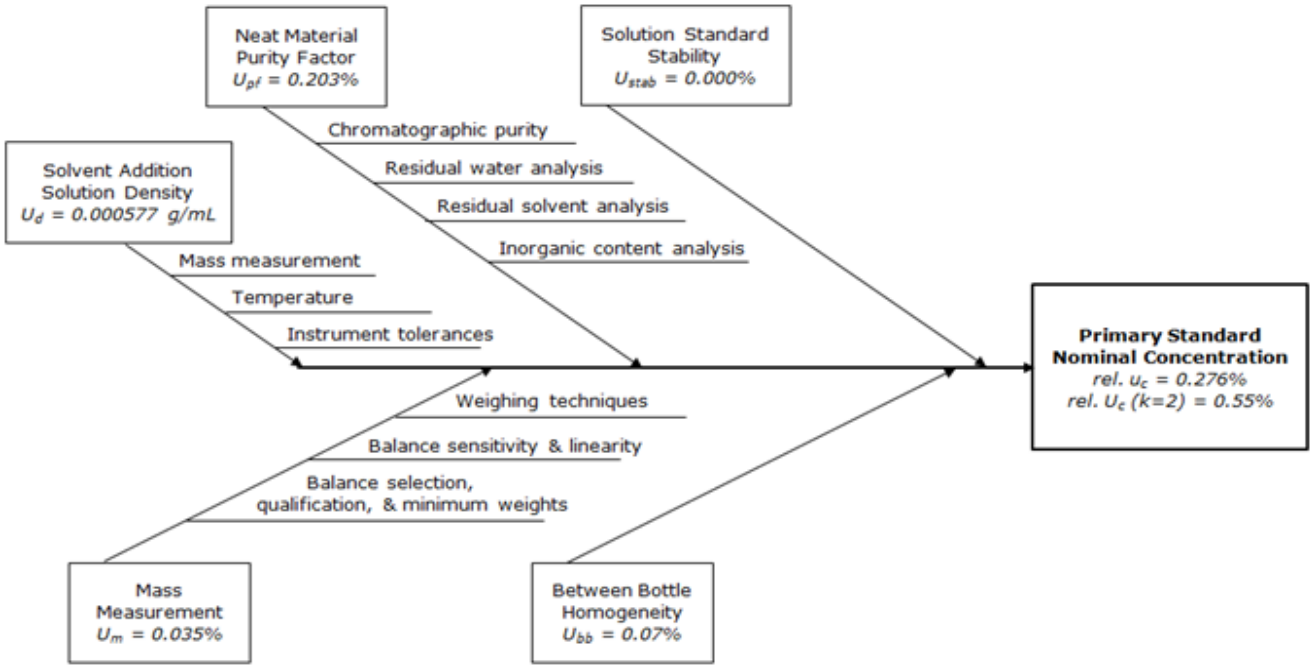
Packaging: 2 mL amber USP Type 1 glass ampoule containing not less than 1 mL of certified solution. Ampoules are overfilled to ensure a minimum of 1 mL volume can be transferred when using a 1mL Class A volumetric pipette.

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.



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Details on metrological traceability:

- This standard has been gravimetrically prepared using balances that have been fully qualified and calibrated to ISO 17025 requirements. All calibrations utilize NIST traceable weights which are calibrated externally by a qualified ISO 17025 accredited calibration laboratory to NIST standards. Qualification of each balance includes the assignment of a minimum weighing by a qualified and ISO 17025 accredited calibration vendor taking into consideration the balance and installed environmental conditions to ensure compliance with USP tolerances of NMT 0.10% relative error.
- Fill volume to predetermined specifications is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- The density and material Mass Balance Purity Factor of each raw material is traceable to the SI and higher order reference materials through mass measurement and instrument qualification and calibrations.

Details about certification process:

This standard has been prepared and certified under the ISO 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.

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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 (mg/mL)	**%RSD - Homogeneity**
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.

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Analyte Certification - Mass Balance Purity Factor

Each analyte is thoroughly identified and characterized using an orthogonal approach. A mass balance purity factor is assigned incorporating chromatographic purity and residual impurities. The mass balance purity factor is utilized to calculate the weighing adjustment necessary to ensure accuracy of the solution standard concentration.

Material Name:	para-Fluorobutyryl fentanyl-$^{13}C_6$	**Chemical Formula:**	$C_{17}{}^{13}C_6H_{29}N_2OF$
Material Lot:	FC10151802	**CAS Number:**	NA
		Molecular Weight:	374.44

Material Characterization Summary

Analytical Test	**Method**	**Results**		
Primary Chromatographic Purity by HPLC/UV Analysis	SP10-0102	99.7% [1]		
Secondary Chromatographic Purity by GC/FID Analysis	SP10-0101	99.7%		
Identity by LC/MS Analysis	SP10-0107	Consistent with Structure		
Isotopic Purity and Distribution by LC/MS SIM Analysis	SP10-0107	0.00% $^{13}C_0$ vs $^{13}C_6$		
		0.00% $^{13}C_0$	0.19% $^{13}C_4$	
		0.00% $^{13}C_1$	4.05% $^{13}C_5$	
		0.00% $^{13}C_2$	99.76% $^{13}C_6$	
		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 [2]	None Detected		
Residual Water Analysis by Karl Fischer Coulometry	AM1346 [2]	Below Quantitation Limit		
Elemental Analysis	Outsourced		Calculated	Analyzed
		C	54.53%	74.08%
		H	7.81%	7.62%
		N	7.48%	7.67%
Mass Balance Purity Factor		99.66%		

[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.

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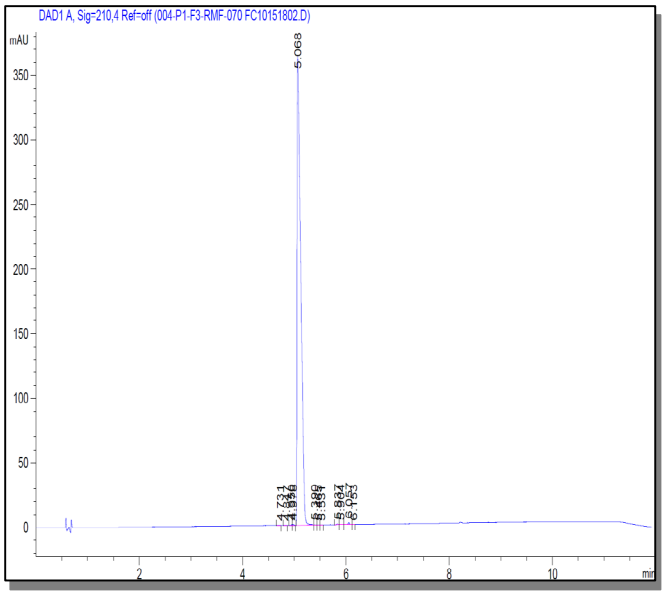
Spectral and Physical Data

HPLC/UV



Column: Ascentis Express C18, 2.7 µm, 3.0 x 100 mm

Mobile Phase: A: Acetonitrile
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/min

Wavelength: 210 nm

Sample Name: FC10151802

Acquired: February 26, 2019

Peak #	Ret Time	Area %
1	4.73	0.01
2	4.85	0.01
3	4.95	0.04
4	4.98	0.05
5	5.07	99.62
6	5.39	0.02
7	5.47	0.01
8	5.53	0.01
9	5.84	0.05
10	5.90	0.03
11	6.06	0.15
12	6.15	0.01

Peak 4 is identified as Butyryl fentanyl

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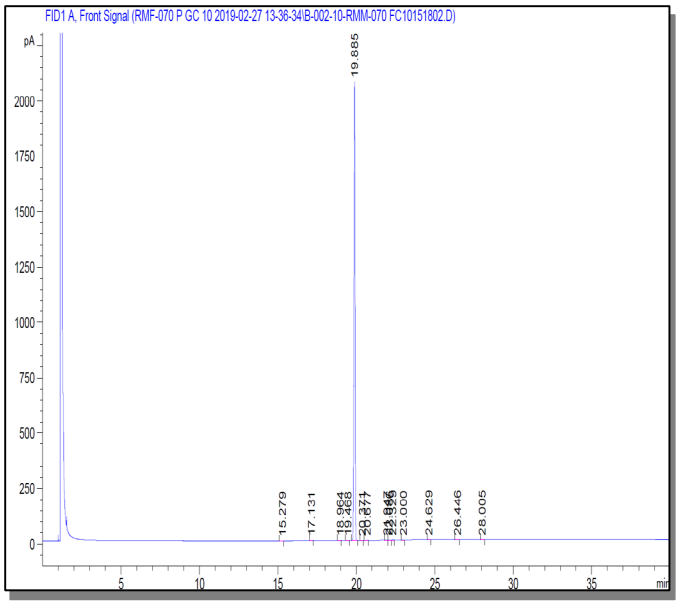
Spectral and Physical Data (cont.)

GC/FID

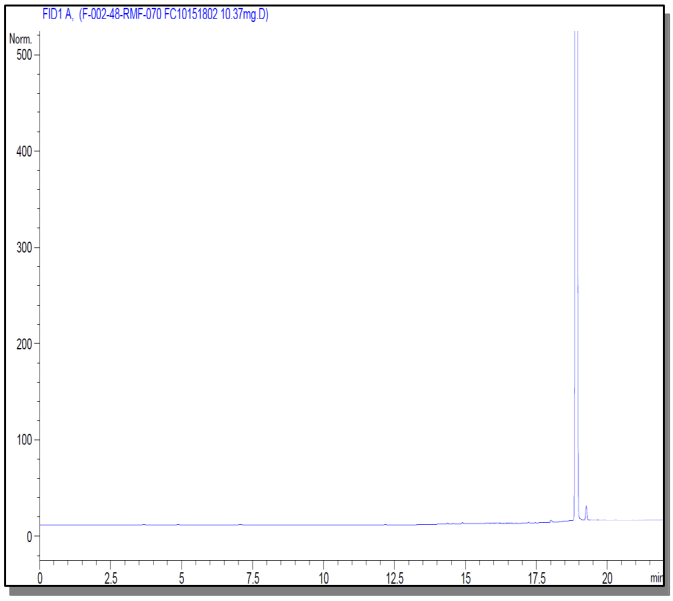


Column: DB-5ms, 30 m x 0.53 mm ID, 1.5 µm film thickness
Temp Program: 40°C to 200°C at 40°C/min
200°C to 300°C at 5°C/min
hold 16 min
Injector Temp: Cool-on-Column
Detector Temp: 325°C

Sample Name: FC10151802
Acquired: February 27, 2019

Peak #	Ret Time	Area %
1	15.28	0.01
2	17.13	0.01
3	18.96	0.01
4	19.47	0.01
5	19.89	99.74
6	20.37	0.01
7	20.68	0.03
8	21.95	0.01
9	22.09	0.01
10	22.33	0.11
11	23.00	0.02
12	24.63	0.01
13	26.45	0.01
14	28.01	0.01

Residual Solvent Analysis by GC/FID Headspace



Column: DB-ALC1 30 m x 0.53 mm, 3 µm film thickness
Temp Program: 40°C hold 12 min to 220°C at 40°C/min hold 5.5 min
Carrier Gas: Helium
Flow Rate: 2.0 mL/min
Detector Heater Temp: 250°C
Injector: Headspace Sampler
HS Oven Temp: 60°C
Vial Equilibration: 10 minutes

Sample Name: FC10151802
Acquired: February 27, 2019

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

ND - None Detected

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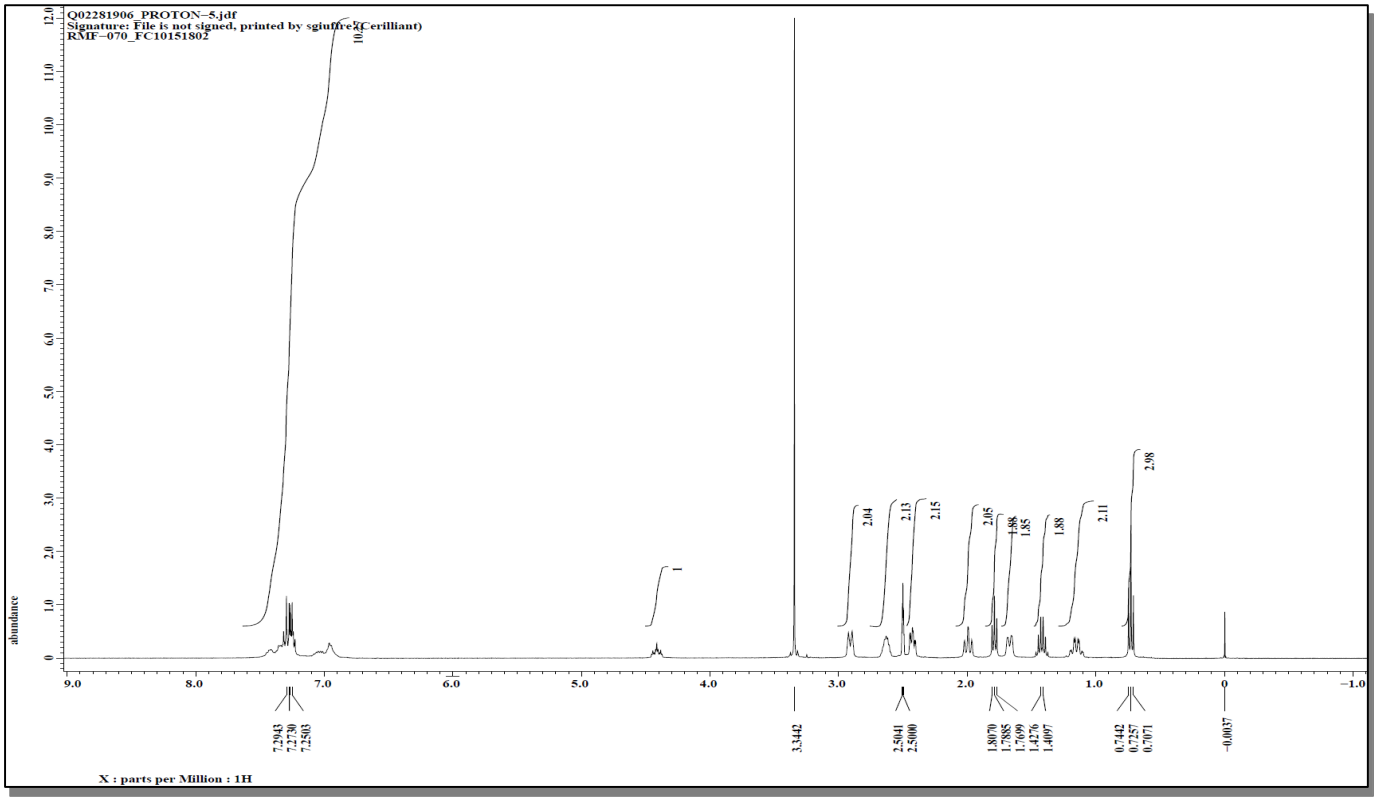
Spectral and Physical Data (cont.)

^{1}H NMR

Instrument: JEOL ECS 400
Solvent: DMSO-D_6



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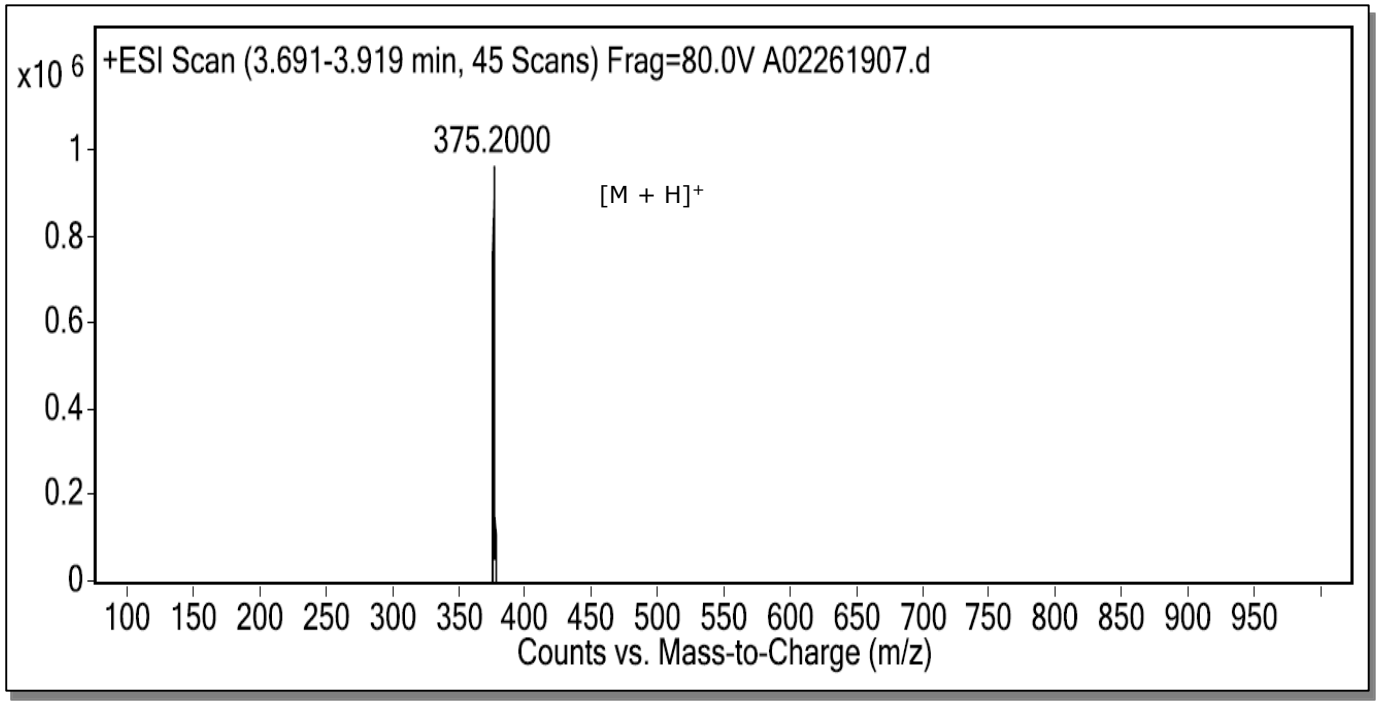
Spectral and Physical Data (cont.)

LC/MS

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



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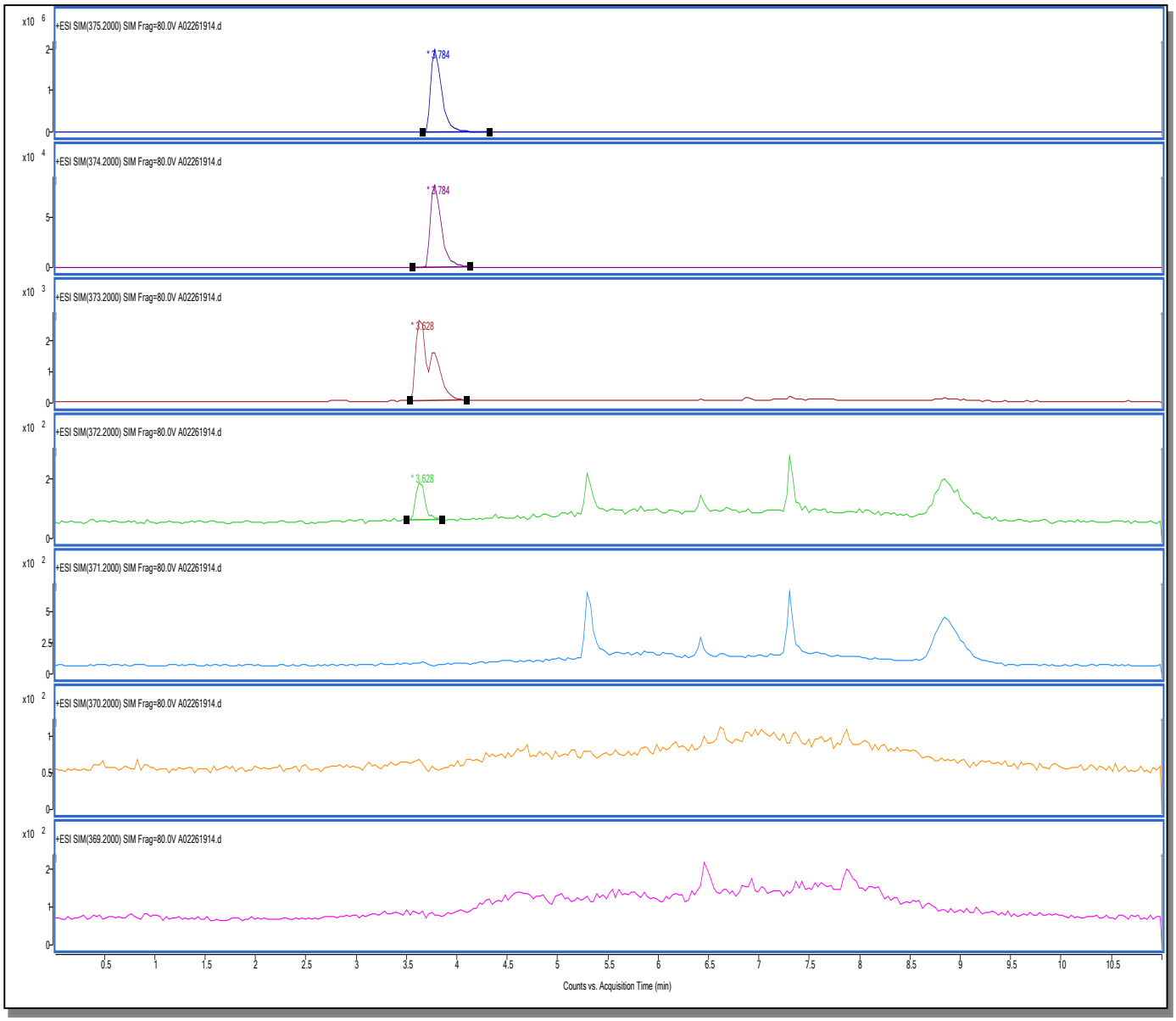
Spectral and Physical Data (cont.)

Isotopic Purity by LC/MS SIM

Column: Kinetex C18, 2.6 µm, 2.1 x 50 mm
Mobile Phase: A: 0.1% Formic acid in Water
B: Acetonitrile
Gradient:

Time (min)	% A	% B
0.0	80	20
5.0	20	80
6.0	20	80
7.0	80	20
11.0	80	20

Flow Rate: 0.5 mL/min
Scan Range: 369-375 amu
Ionization: Electrospray, Negative Ion
Instrument: Agilent 6410A Mass Spectrometer
Acquired: February 26, 2019



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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 (F-048-0.5ML, para-Fluorobutyryl fentanyl) is listed below.*

Freezer	-15°C	No decrease in purity was noted after four weeks.
Refrigerator	4°C	
Room Temperature	21°C	
40°C	40°C	

Transport/Shipping: *Stability studies support the transport of this product at ambient conditions.*

Long Term Stability: *Long term stability has been assessed for Freezer storage (-10 °C to -25 °C) conditions. Stability of a minimum of 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.
		Updated Retest Date of May 2020 to February 2021.
02	December 09, 2020	Updated Retest Date of February 2021 to November 2021.

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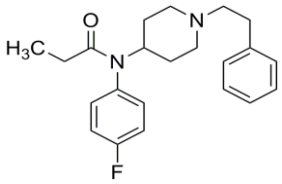
Certified Reference Material - Certificate of Analysis

para-Fluorofentanyl, Primary Measurement Standard

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

Cerilliant Quality
ISO 17034
ISO/IEC 17025
ISO 13485
ISO 14001
ISO 9001

Product No.: F-067-1ML
Lot No.: FC12261801
Description of CRM: para-Fluorofentanyl in Methanol (Solution)
Retest Date: July 2022 See Section "Stability Assessment".
Storage: Store unopened in freezer (-10 °C to -25 °C).
Shipping: Ambient. See Section "Stability Assessment".
Chemical formula: $C_{22}H_{27}FN_2O$
CAS No.: 90736-23-5
Regulatory: USDEA Schedule I/9812



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

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

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

Intended use: This Certified Reference Material is suitable for the in vitro identification, calibration, and quantification of the analyte(s) in analytical and R&D applications. Not suitable for human or animal consumption.

Minimum sample size: 1 µL for quantitative applications

Instructions for handling and correct use: Concentration is corrected for chromatographic purity, residual solvents and residual inorganics. No adjustment required before use.
Users should quantitatively transfer desired volume using established good laboratory practices to spike into matrix or to dilute to the desired concentration. Each ampoule is intended for one-time use.

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

Accreditation: Cerilliant Corp. is accredited by the US accreditation authority ANAB as registered reference material producer AR-1353 in accordance with ISO 17034 and registered testing laboratory AT-1352 according to ISO/IEC 17025.

Darron Ellsworth, Quality Assurance Manager

February 06, 2020
Issue Date

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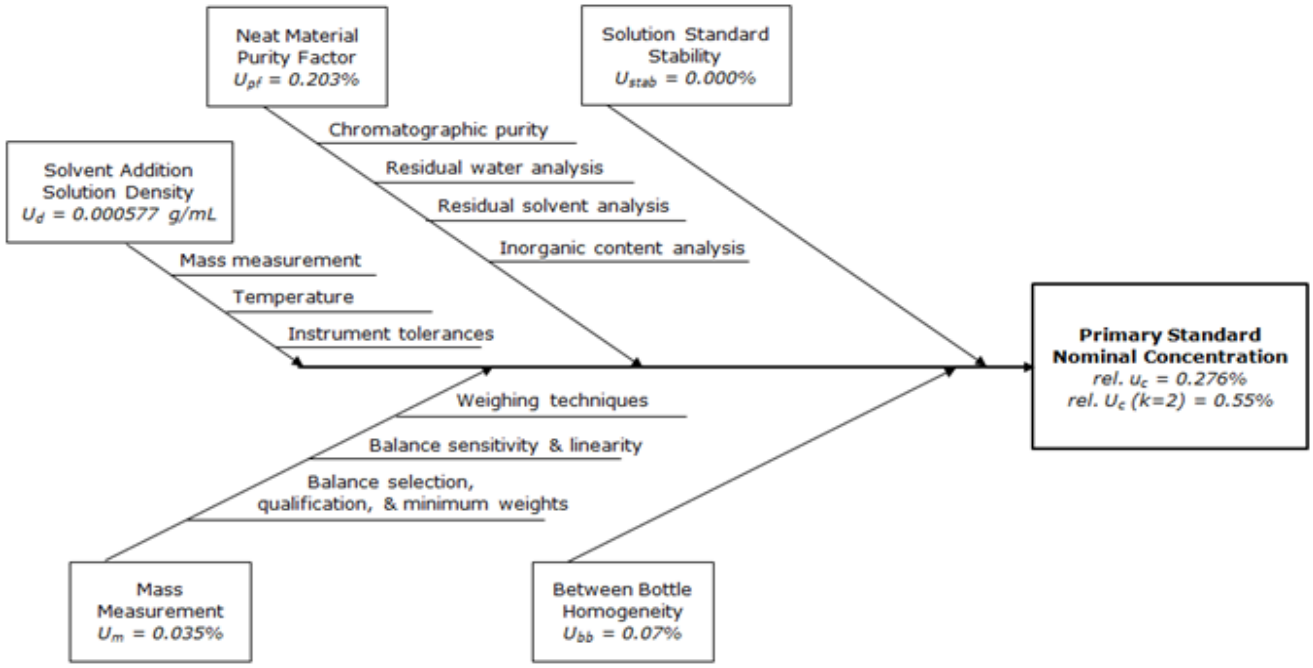
Packaging:	2 mL amber USP Type 1 glass ampoule containing not less than 1 mL of certified solution. Ampoules are overfilled to ensure a minimum of 1 mL volume can be transferred when using a 1mL Class A volumetric pipette.
Details on starting materials:	Each raw material utilized has been identified 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.



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Details on metrological traceability:

- This standard has been gravimetrically prepared using balances that have been fully qualified and calibrated to ISO 17025 requirements. All calibrations utilize NIST traceable weights which are calibrated externally by a qualified ISO 17025 accredited calibration laboratory to NIST standards. Qualification of each balance includes the assignment of a minimum weighing by a qualified and ISO 17025 accredited calibration vendor taking into consideration the balance and installed environmental conditions to ensure compliance with USP tolerances of NMT 0.10% relative error.
- Fill volume to predetermined specifications is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- The density and material Mass Balance Purity Factor of each raw material is traceable to the SI and higher order reference materials through mass measurement and instrument qualification and calibrations.

Details about certification process:

This standard has been prepared and certified under the ISO 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 (mg/mL)	**%RSD - 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:	para-Fluorofentanyl	**Chemical Formula:**	$C_{22}H_{27}FN_2O$
Material Lot:	FC10011802	**CAS Number:**	90736-23-5
		Molecular Weight:	354.46

Material Characterization Summary

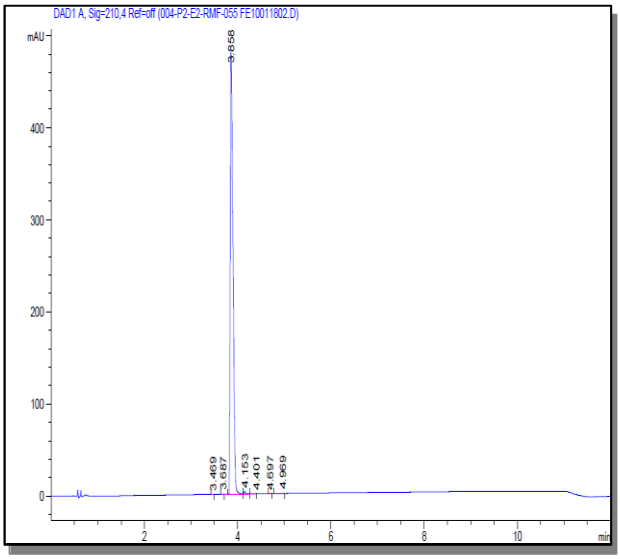
Analytical Test	**Method**	**Results**		
Primary Chromatographic Purity by HPLC/UV Analysis	SP10-0102	99.6% [1]		
Secondary Chromatographic Purity by GC/FID Analysis	SP10-0101	99.8% [2]		
Identity by LC/MS Analysis	SP10-0107	Consistent with Structure		
Identity by ^{1}H-NMR Analysis	USP <761>, SP10-0116	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		
Elemental Analysis	Outsourced		Calculated	Analyzed
		C	74.55%	74.38%
		H	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 Express C18, 2.7 µm, 3.0 x 100 mm

Mobile Phase: A: Acetonitrile
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/min

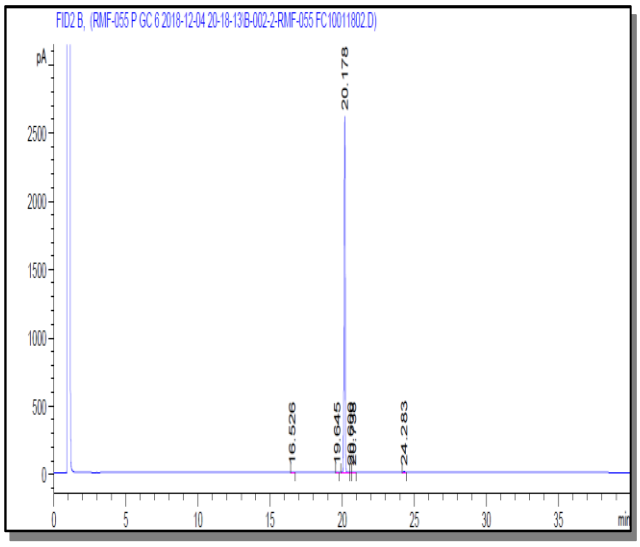
Wavelength: 210 nm

Sample Name: FC10011802

Acquired: December 05, 2018

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

GC/FID



Column: DB-35ms, 30 m x 0.53 mm ID, 1.0 µm film thickness

Temp Program: 40°C to 200°C at 40°C/min
200°C to 300°C at 5°C/min
hold 16 min

Injector Temp: Cool-on-Column

Detector Temp: 325°C

Sample Name: FC10011802

Acquired: 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

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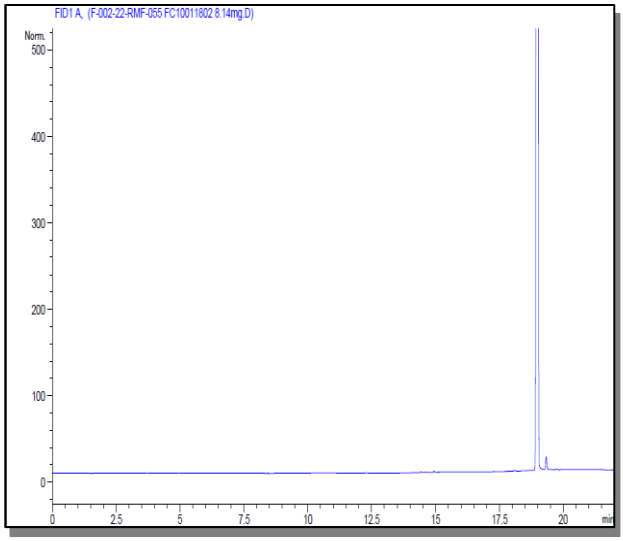
Spectral and Physical Data (cont.)

Residual Solvent Analysis by GC/FID Headspace



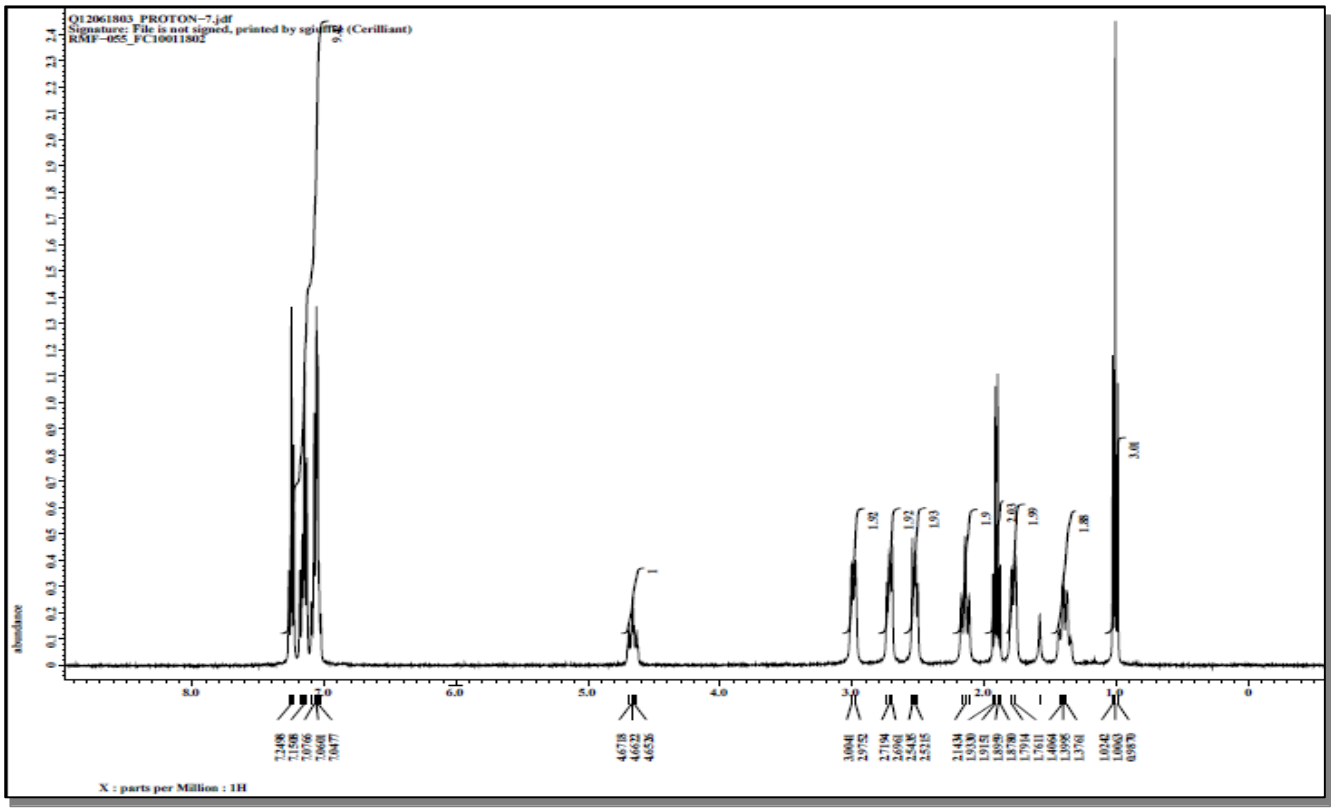
Column:	DB-ALC1 30 m x 0.53 mm, 3 µm film thickness
Temp Program:	40°C hold 12 min to 220°C at 40°C/min hold 5.5 min
Carrier Gas:	Helium
Flow Rate:	2.0 mL/min
Detector Heater Temp:	250°C
Injector:	Headspace Sampler
HS Oven Temp:	60°C
Vial Equilibration:	10 minutes
Sample Name:	FC10011802
Acquired:	December 06, 2018

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

ND - None Detected

^{1}H NMR

Instrument: JEOL ECS 400
Solvent: Chloroform-D



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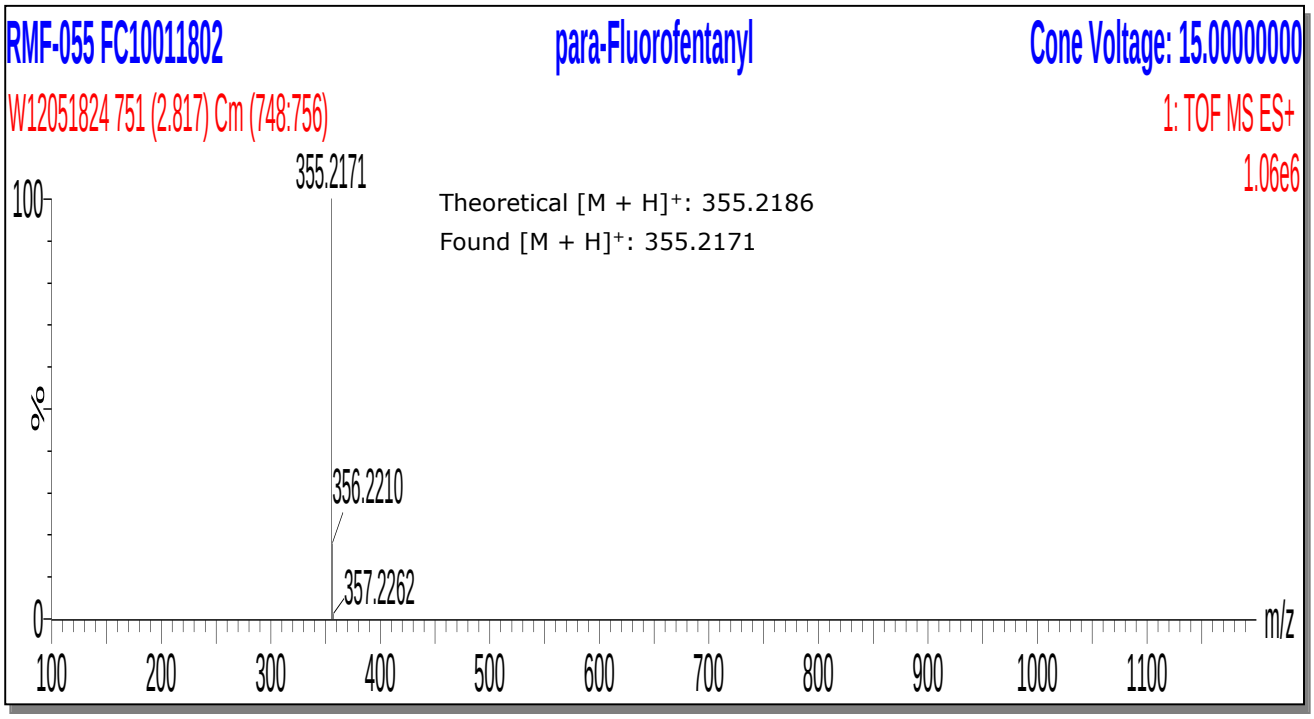
Spectral and Physical Data (cont.)

LC/MS

Column:	Ascentis Express C18, 2.7 µm, 3.0 x 50 mm	**Flow Rate:**	0.4 mL/min
Mobile Phase:	A: 0.1% Formic acid in Water B: Acetonitrile	**Scan Range:**	100-1200 amu
		Ionization:	Electrospray, Positive Ion
		Instrument:	Waters XEVO G2 QTOF
Gradient:		**Acquired:**	December 05, 2018

Time (min)	% A	% B
0.0	90	10
0.5	90	10
4.0	50	50
5.8	50	50
6.0	90	10
8.0	90	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 this product is listed below.*

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

Transport/Shipping: *Stability studies support the transport of this product at ambient conditions.*

Long Term Stability: *Long term stability has been assessed for Freezer storage (-10 °C to -25 °C) conditions. Stability of a minimum of 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.

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Certified Reference Material - Certificate of Analysis

para-Fluorofentanyl-$^{13}C_6$, Primary Measurement Standard

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

Product No.: F-068-1ML
Lot No.: FC01141904
Description of CRM: para-Fluorofentanyl-$^{13}C_6$ in Methanol (Solution)
Retest Date: November 2021 See Section "Stability Assessment".
Storage: Store unopened in freezer (-10 °C to -25 °C).
Shipping: Ambient. See Section "Stability Assessment".
Chemical formula: $C_{16}{}^{13}C_6H_{27}N_2OF$
CAS No.: NA
Regulatory: USDEA Schedule I

Cerilliant Quality
ISO 17034
ISO/IEC 17025
ISO 13485
ISO 14001
ISO 9001

Analyte	Certified Concentration ± associated uncertainty U, u=k*u (k=2)
para-Fluorofentanyl-$^{13}C_6$	**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.
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

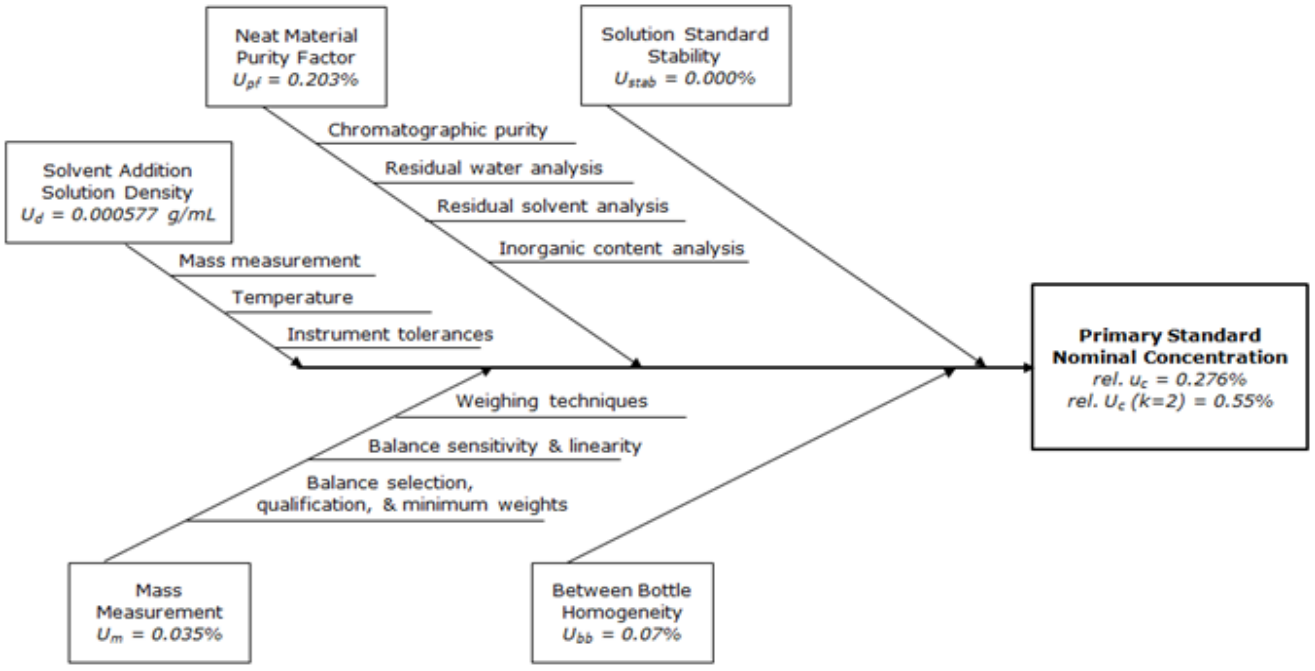
December 10, 2020
Issue Date

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 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**
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:	para-Fluorofentanyl-$^{13}C_6$	**Chemical Formula:**	$C_{16}{}^{13}C_6H_{27}N_2OF$
Material Lot:	FC10151801	**CAS Number:**	NA
		Molecular Weight:	360.42

Material Characterization Summary

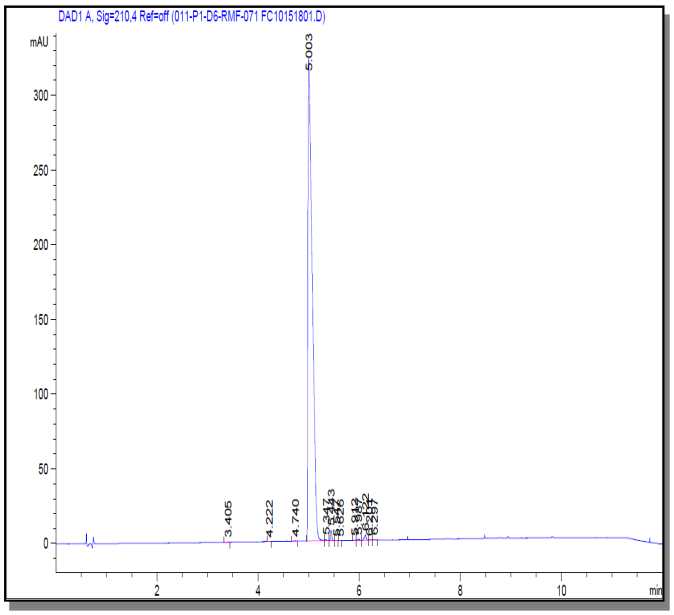
Analytical Test	**Method**	**Results**	
Primary Chromatographic Purity by HPLC/UV Analysis	SP10-0102	98.4%	
Secondary Chromatographic Purity by GC/FID Analysis	SP10-0101	98.7%	
Identity by LC/MS Analysis	SP10-0107	Consistent with Structure	
Isotopic Purity and Distribution by LC/MS SIM Analysis	SP10-0107	0.00% $^{13}C_0$ vs $^{13}C_6$	
		0.00% $^{13}C_0$ to $^{13}C_1$	2.80% $^{13}C_5$
		0.03% $^{13}C_2$ to $^{13}C_3$	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%	

[1] Validated analytical method

- The primary chromatographic purity is calculated as the average of two independently performed analyses utilizing two different methods. Acceptance criteria requires the purity values to be within 0.5% of each other.
- The primary purity method was selected to optimize resolution of impurities while minimizing degradation of the analyte. Secondary purity methods with orthogonal detector capabilities from the primary purity method are used as controls to confirm an accurate purity value.
- The primary chromatographic purity value is used to calculate the Mass Balance Purity Factor.
- A secondary chromatographic purity method is utilized as a control.
- Mass Balance Purity Factor = [(100 - wt% residual solvent - wt% residual water - wt% residual inorganics) x Chromatographic Purity/100].
- Mass Balance Purity Factor does not include adjustment for chiral and/or isotopic purity.

Spectral and Physical Data

HPLC/UV



Column: Ascentis Express Phenyl-Hexyl, 2.7 µm, 3.0 x 100 mm

Mobile Phase: A: Acetonitrile
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/min

Wavelength: 210 nm

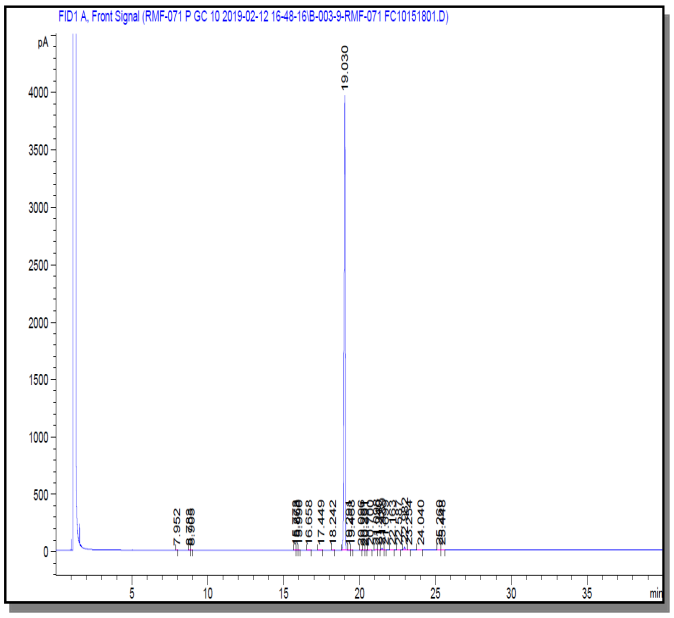
Sample Name: FC10151801

Acquired: February 11, 2019

Peak #	Ret Time	Area %
1	3.41	0.01
2	4.22	0.01
3	4.74	0.03
4	5.00	98.49
5	5.35	0.09
6	5.44	0.68
7	5.55	0.01
8	5.63	0.01
9	5.91	0.03
10	5.99	0.11
11	6.12	0.47
12	6.20	0.01
13	6.30	0.05

Spectral and Physical Data (cont.)

GC/FID



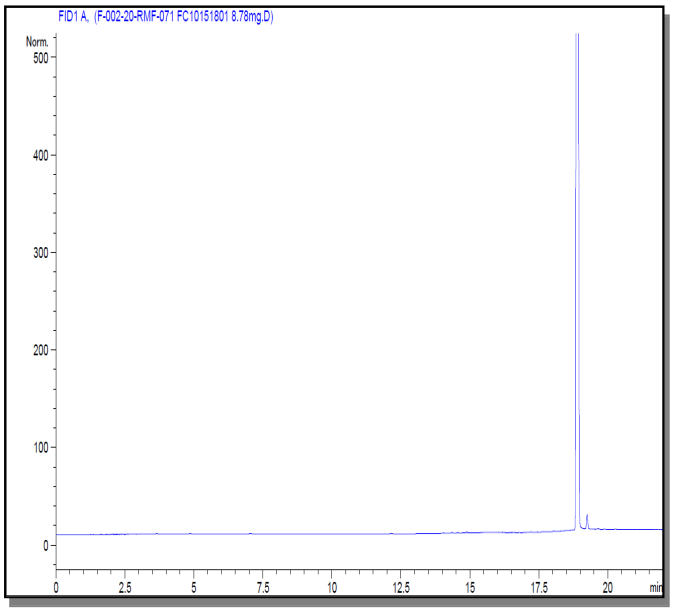
Column: DB-5ms, 30 m x 0.53 mm ID, 1.5 µm film thickness
Temp Program: 40°C to 200°C at 40°C/min
200°C to 300°C at 5°C/min
hold 16 min
Injector Temp: Cool-on-Column
Detector Temp: 325°C

Sample Name: FC10151801
Acquired: February 12, 2019

Peak #	Ret Time	Area %
1	7.95	0.00
2	8.78	0.00
3	8.91	0.00
4	15.77	0.03
5	15.87	0.01
6	15.99	0.01
7	16.66	0.01
8	17.45	0.02
9	18.24	0.00
10	19.03	98.65
11	19.29	0.01
12	19.47	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

Spectral and Physical Data (cont.)

Residual Solvent Analysis by GC/FID Headspace



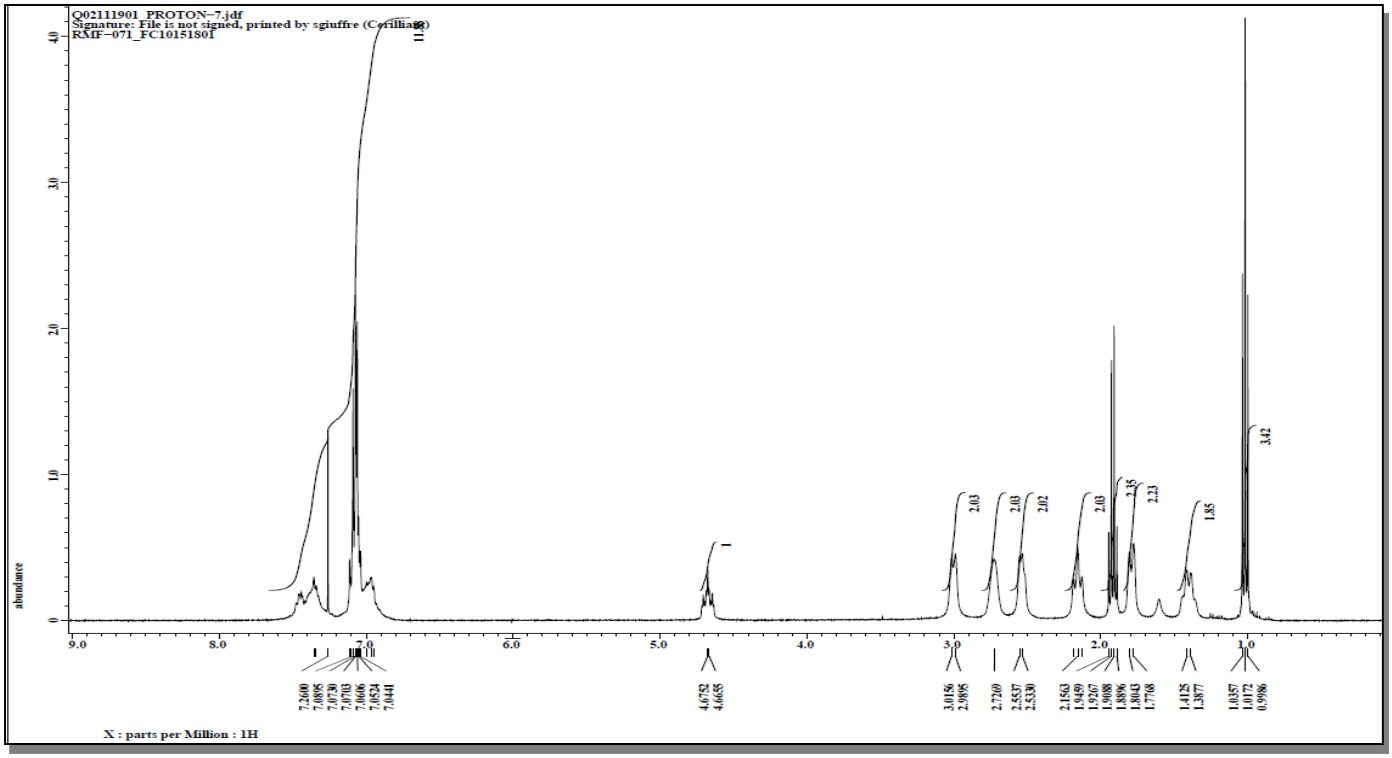
Column:	DB-ALC1 30 m x 0.53 mm, 3 µm film thickness
Temp Program:	40°C hold 12 min to 220°C at 40°C/min hold 5.5 min
Carrier Gas:	Helium
Flow Rate:	2.0 mL/min
Detector Heater Temp:	250°C
Injector:	Headspace Sampler
HS Oven Temp:	60°C
Vial Equilibration:	10 minutes
Sample Name:	FC10151801
Acquired:	February 14, 2019

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

ND - None Detected

^{1}H NMR

Instrument:	JEOL ECS 400
Solvent:	Chloroform-D



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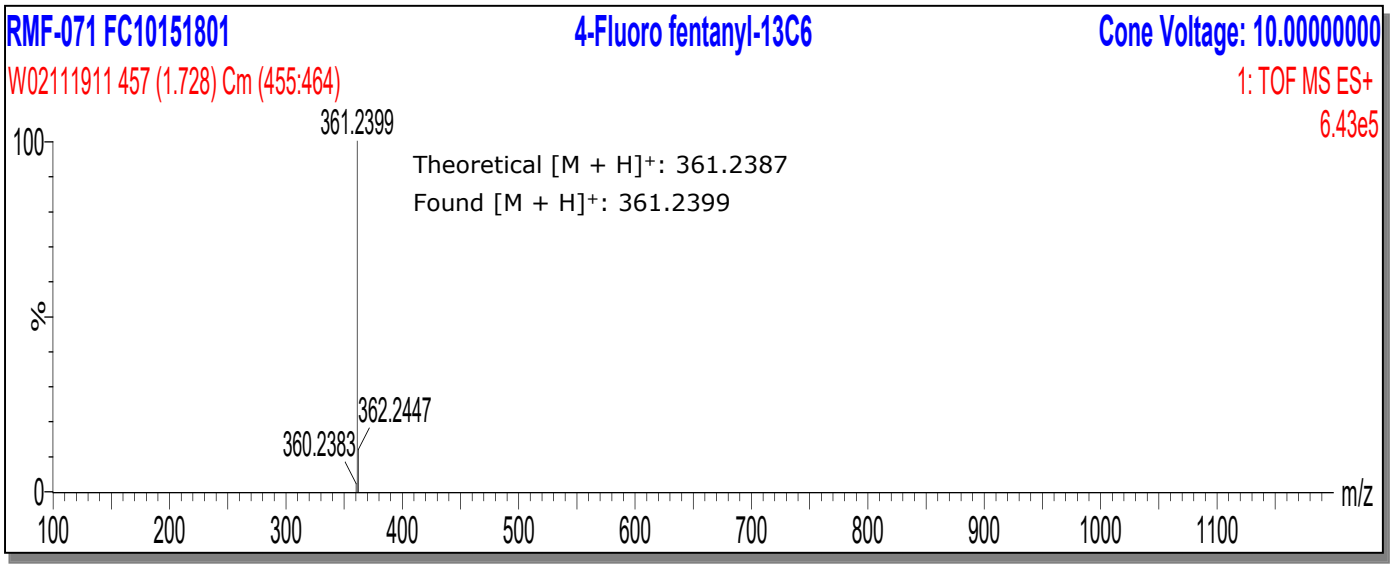
Spectral and Physical Data (cont.)

LC/MS

Column:	Ascentis Express C18, 2.7 µm, 3.0 x 50 mm	**Flow Rate:**	0.4 mL/min
Mobile Phase:	A: 0.1% Formic acid in Water B: Acetonitrile	**Scan Range:**	100-1200 amu
		Ionization:	Electrospray, Positive Ion
		Instrument:	Waters XEVO G2 QTOF
Gradient:		**Acquired:**	February 11, 2019

Time (min)	% A	% B
0.0	80	20
0.5	80	20
4.0	20	80
5.8	20	80
6.0	80	20
8.0	80	20



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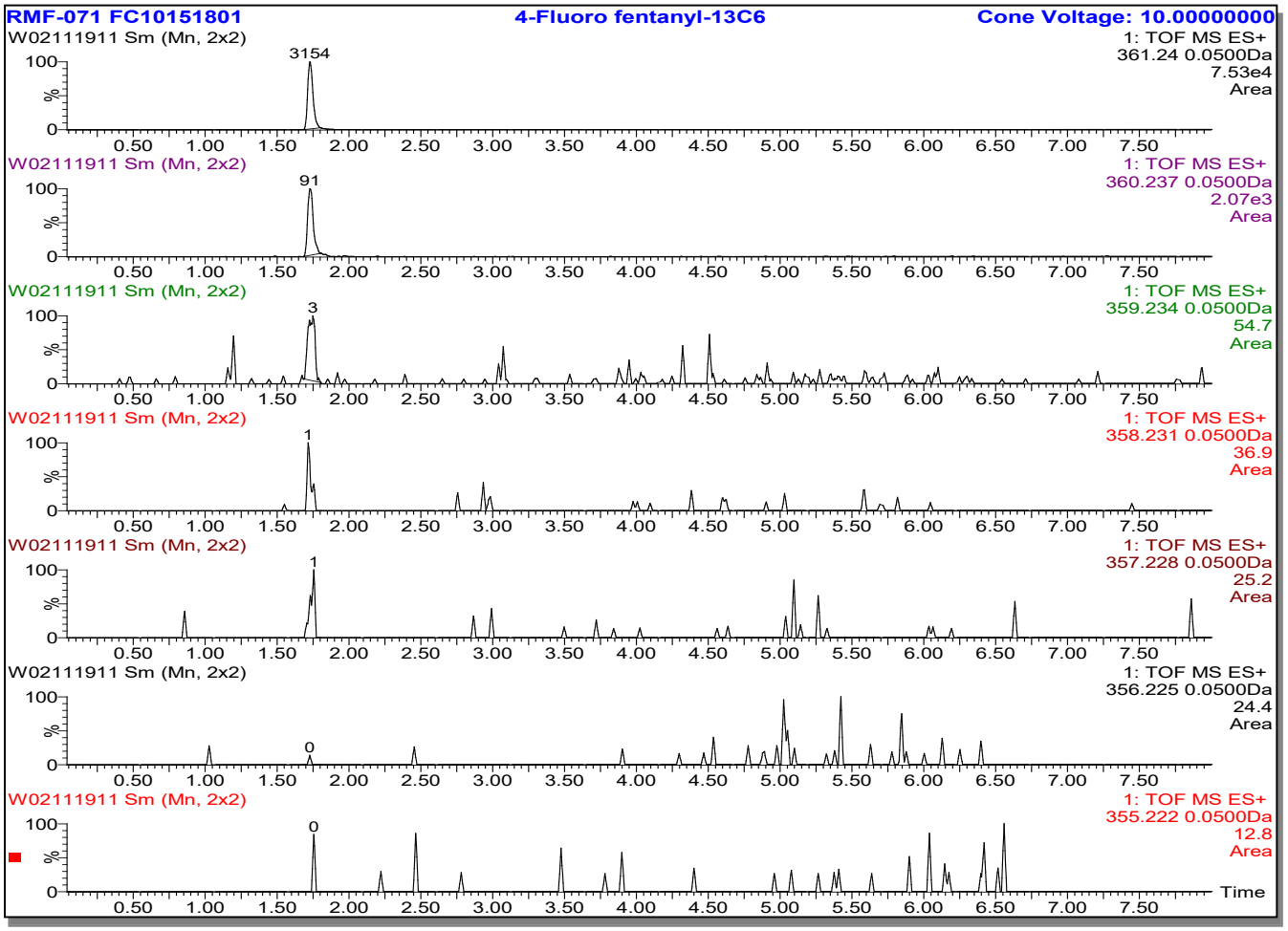
Spectral and Physical Data (cont.)

Isotopic Purity by LC/MS

Column:	Ascentis Express C18, 2.7 µm, 3.0 x 50 mm	**Flow Rate:**	0.4 mL/min
Mobile Phase:	A: 0.1% Formic acid in Water B: Acetonitrile	**Scan Range:**	355-361 amu
		Ionization:	Electrospray, Positive Ion
		Instrument:	Waters XEVO G2 QTOF
Gradient:		**Acquired:**	February 11, 2019

Time (min)	% A	% B
0.0	80	20
0.5	80	20
4.0	20	80
5.8	20	80
6.0	80	20
8.0	80	20



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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 (F-049-0.5ML, para-Fluorofentanyl) is listed below.*

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

Transport/Shipping: *Stability studies support the transport of this product at ambient conditions.*

Long Term Stability: *Long term stability has been assessed for Freezer storage (-10 °C to -25 °C) conditions. Stability of a minimum of 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	April 17, 2020	Updated Retest Date of May 2020 to February 2021.
		Added Long Term Stability data.
02	December 10, 2020	Updated Retest Date of February 2021 to November 2021.

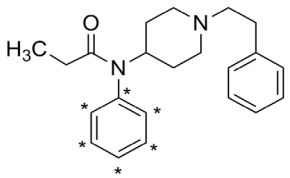
Certified Reference Material - Certificate of Analysis

Fentanyl-$^{13}C_6$, Primary Measurement Standard

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

Cerilliant Quality
ISO 17034
ISO/IEC 17025
ISO 13485
ISO 14001
ISO 9001

Product No.: F-069-1ML
Lot No.: FC01071903
Description of CRM: Fentanyl-$^{13}C_6$ in Methanol (Solution)
Retest Date: October 2021 See Section "Stability Assessment".
Storage: Store unopened in freezer (-10 °C to -25 °C).
Shipping: Ship Ambient. See Section "Stability Assessment".
Chemical formula: $C_{16}{}^{13}C_6H_{28}N_2O$
CAS No.: NA
Regulatory: USDEA Schedule II/9801



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

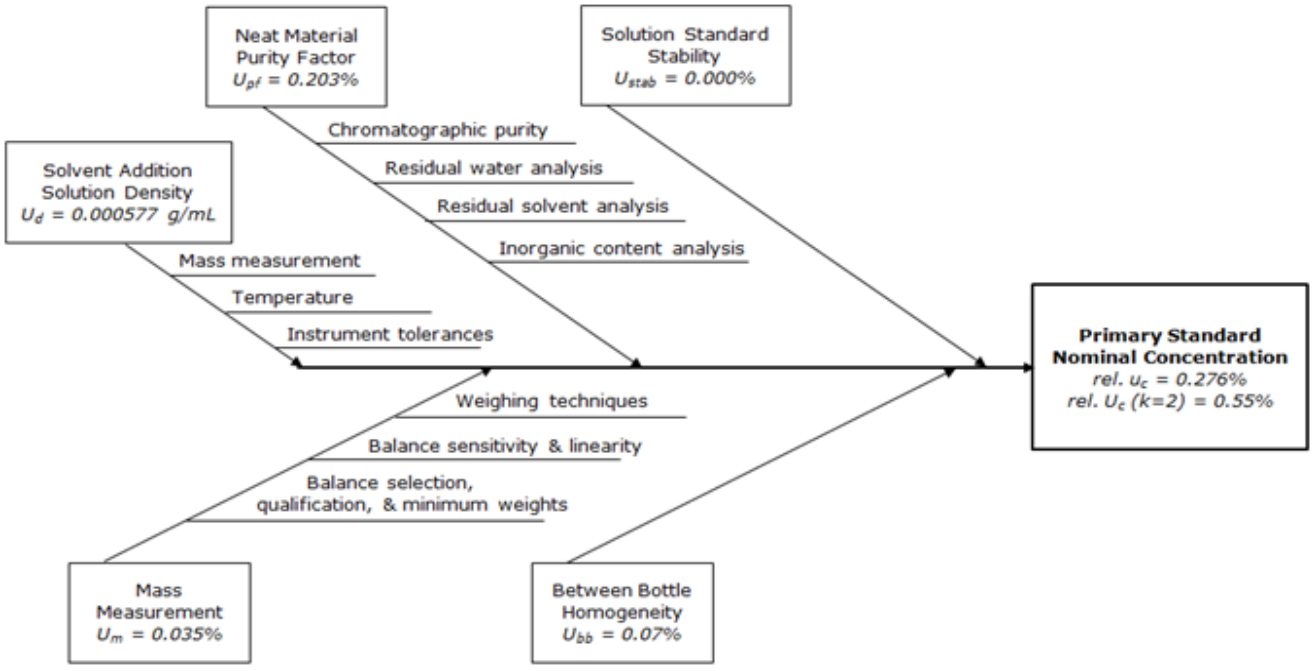
October 27, 2020
Issue Date

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.



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Details on metrological traceability:

- This standard has been gravimetrically prepared using balances that have been fully qualified and calibrated to ISO 17025 requirements. All calibrations utilize NIST traceable weights which are calibrated externally by a qualified ISO 17025 accredited calibration laboratory to NIST standards. Qualification of each balance includes the assignment of a minimum weighing by a qualified and ISO 17025 accredited calibration vendor taking into consideration the balance and installed environmental conditions to ensure compliance with USP tolerances of NMT 0.10% relative error.
- Fill volume to predetermined specifications is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- The density and material Mass Balance Purity Factor of each raw material is traceable to the SI and higher order reference materials through mass measurement and instrument qualification and calibrations.

Details about certification process:

This standard has been prepared and certified under the ISO 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.

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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 Concentration (mg/mL)	**%RSD - Homogeneity**
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.

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Analyte Certification - Mass Balance Purity Factor

Each analyte is thoroughly identified and characterized using an orthogonal approach. A mass balance purity factor is assigned incorporating chromatographic purity and residual impurities. The mass balance purity factor is utilized to calculate the weighing adjustment necessary to ensure accuracy of the solution standard concentration.

Material Name:	Fentanyl-$^{13}C_6$	**Chemical Formula:**	$C_{16}{}^{13}C_6H_{28}N_2O$
Material Lot:	FC10091801	**CAS Number:**	NA
		Molecular Weight:	342.43

Material Characterization 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	
Isotopic Purity and Distribution by LC/MS SIM Analysis	SP10-0107	0.00% $^{13}C_0$ vs $^{13}C_6$	
		0.00% $^{13}C_0$	0.05% $^{13}C_4$
		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 with Structure	
Residual Solvent Analysis by GC/FID Headspace	AM1087 [3]	0.12%	
Residual Water Analysis by Karl Fischer Coulometry	AM1346 [3]	Not Detected	
Inorganic Content by Microash Analysis	SP10-0135	< 0.2%	
Mass Balance Purity Factor		99.08%	

[1] No 4-ANPP-$^{13}C_6$ detected by HPLC/UV analysis.
[2] 0.01% 4-ANPP-$^{13}C_6$ 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.

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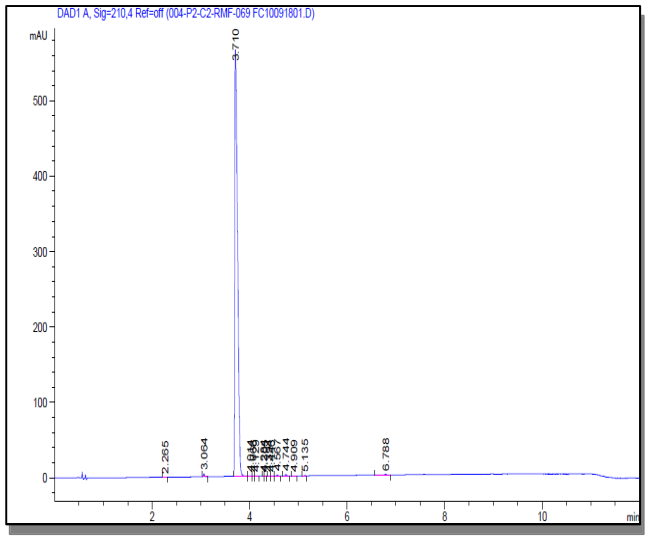
Spectral and Physical Data

HPLC/UV



Column: Ascentis Express C18, 2.7 µm, 3.0 x 100 mm

Mobile Phase: A: Acetonitrile
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/min

Wavelength: 210 nm

Sample Name: FC10091801

Acquired: December 19, 2018

Peak #	Ret Time	Area %
1	2.27	0.01
2	3.06	0.28
3	3.71	99.20
4	4.01	0.05
5	4.07	0.01
6	4.13	0.02
7	4.28	0.01
8	4.31	0.02
9	4.39	0.01
10	4.45	0.01
11	4.57	0.09
12	4.74	0.14
13	4.91	0.01
14	5.14	0.01
15	6.79	0.11

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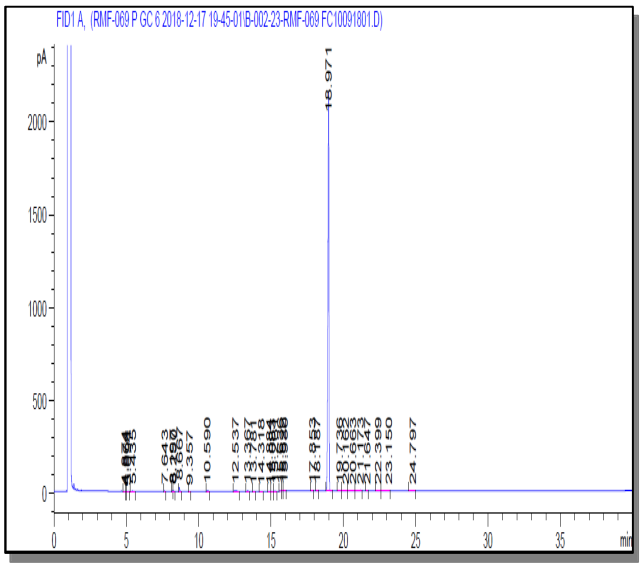
Spectral and Physical Data (cont.)

GC/FID



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

Sample Name: FC10091801
Acquired: 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-$^{13}C_6$

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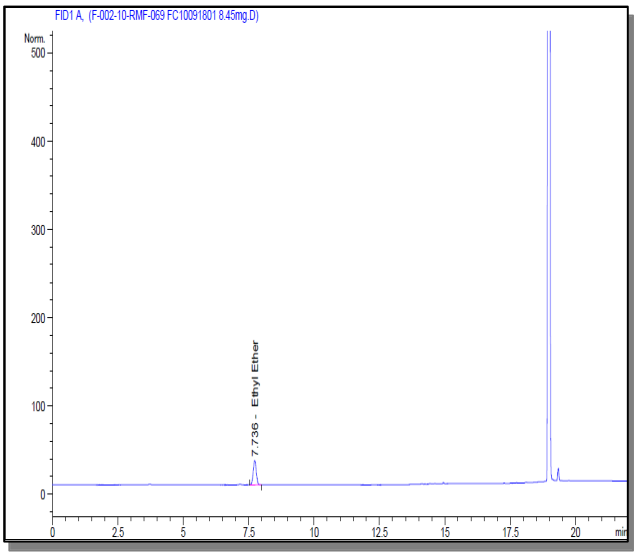
Spectral and Physical Data (cont.)

Residual Solvent Analysis by GC/FID Headspace

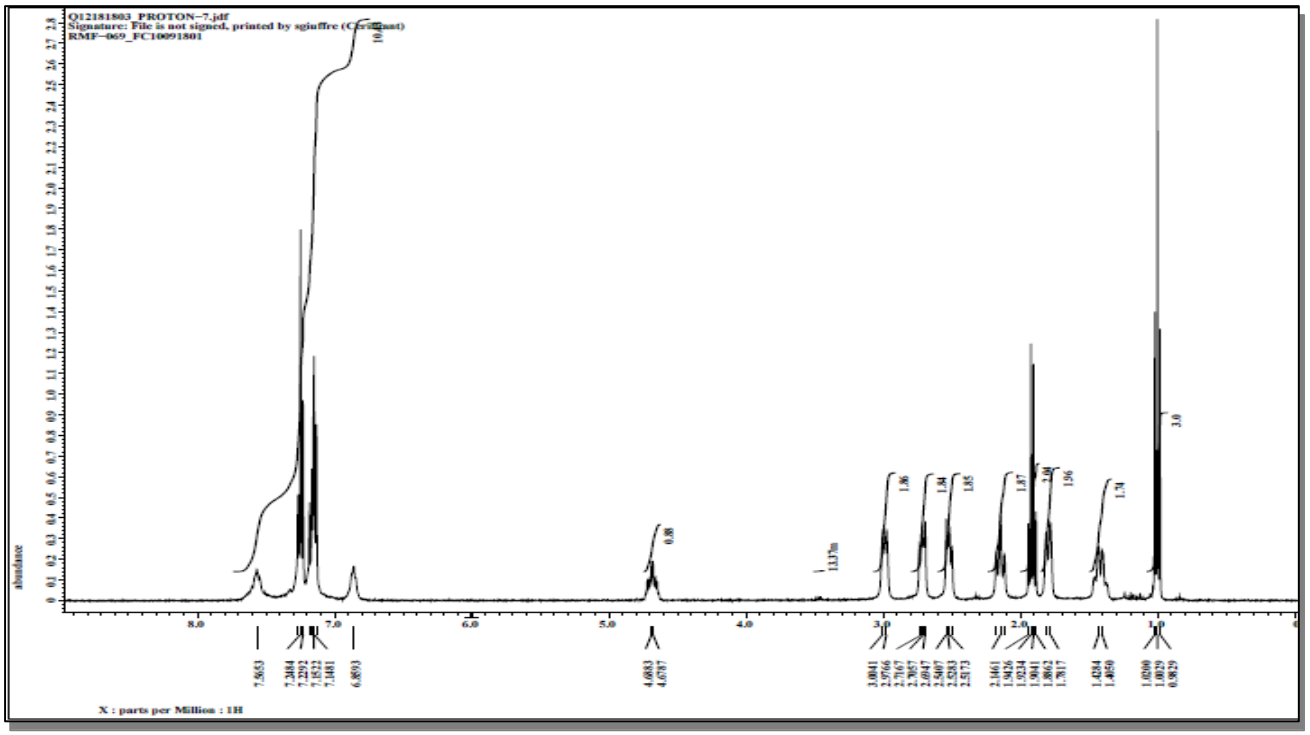


Column:	DB-ALC1 30 m x 0.53 mm, 3 µm film thickness
Temp Program:	40°C hold 12 min to 220°C at 40°C/min hold 5.5 min
Carrier Gas:	Helium
Flow Rate:	2.0 mL/min
Detector Heater Temp:	250°C
Injector:	Headspace Sampler
HS Oven Temp:	60°C
Vial Equilibration:	10 minutes
Sample Name:	FC10091801
Acquired:	December 19, 2018

Peak	Compound	Area	Weight %
1	Ethyl ether	222.75	0.12
2	NMP	NA	NA
Total			**0.12**

^{1}H NMR

Instrument:	JEOL ECS 400
Solvent:	Chloroform-D



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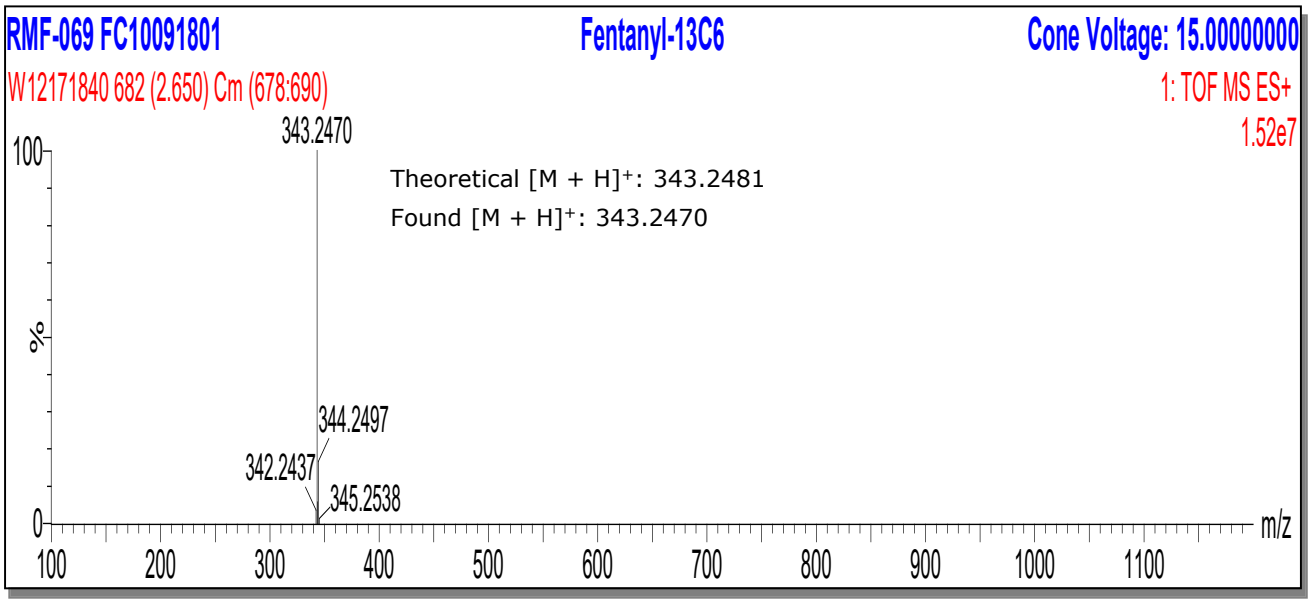
Spectral and Physical Data (cont.)

LC/MS

Column:	Ascentis Express C18, 2.7 µm, 3.0 x 50 mm	**Flow Rate:**	0.4 mL/min
Mobile Phase:	A: 0.1% Formic acid in Water B: Acetonitrile	**Scan Range:**	100-1200 amu
		Ionization:	Electrospray, Positive Ion
		Instrument:	Waters XEVO G2 QTOF
Gradient:		**Acquired:**	December 17, 2018

Time (min)	% A	% B
0.0	90	10
0.5	90	10
4.0	50	50
5.8	50	50
6.0	90	10
8.0	90	10



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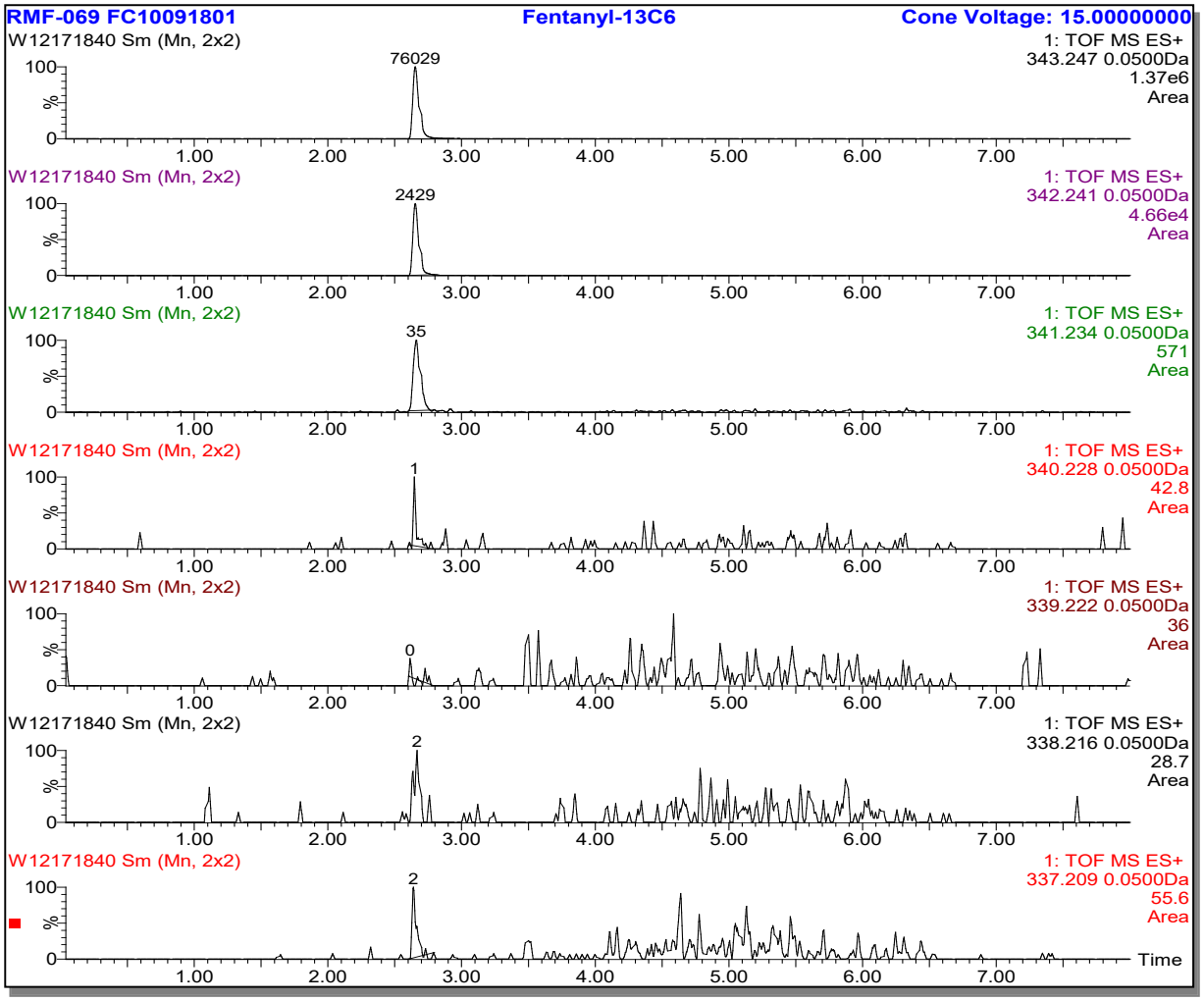
Spectral and Physical Data (cont.)

Isotopic Purity by LC/MS SIM

Column: Ascentis Express C18, 2.7 µm, 3.0 x 50 mm
Mobile Phase: A: 0.1% Formic acid in Water
B: Acetonitrile
Gradient:

Time (min)	% A	% B
0.0	90	10
0.5	90	10
4.0	50	50
5.8	50	50
6.0	90	10
8.0	90	10

Flow Rate: 0.4 mL/min
Scan Range: 337-343 amu
Ionization: Electrospray, Positive Ion
Instrument: Waters XEVO G2 QTOF
Acquired: December 17, 2018



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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 (F-013, Fentanyl) is listed below.*

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

Transport/Shipping: *Stability studies support the transport of this product at ambient conditions.*

Long Term Stability: *Long term stability has been assessed for Freezer storage (-10 °C to -25 °C) conditions. Stability of a minimum of 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.

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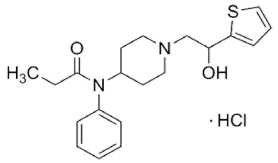
Certified Reference Material - Certificate of Analysis

(±)-beta-Hydroxythiofentanyl, Primary Measurement Standard

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

Product No.:	H-137-1ML
Lot No.:	FC12261806
Description of CRM:	(±)-beta-Hydroxythiofentanyl HCl in Methanol (Solution) Nominal concentration is adjusted for HCl content.
Retest Date:	November 2021 See Section "Stability Assessment".
Storage:	Store unopened in freezer (-10 °C to -25 °C).
Shipping:	Ship cold. See Section "Stability Assessment".
Chemical formula:	$C_{20}H_{26}N_2O_2S \bullet HCl$
CAS No.:	NA
Regulatory:	USDEA Schedule I

Cerilliant Quality
ISO 17034
ISO/IEC 17025
ISO 13485
ISO 14001
ISO 9001



Analyte	Certified Concentration ± associated uncertainty U, u=k*u (k=2)
(±)-beta-Hydroxythiofentanyl	**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.

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 15, 2020
Issue Date

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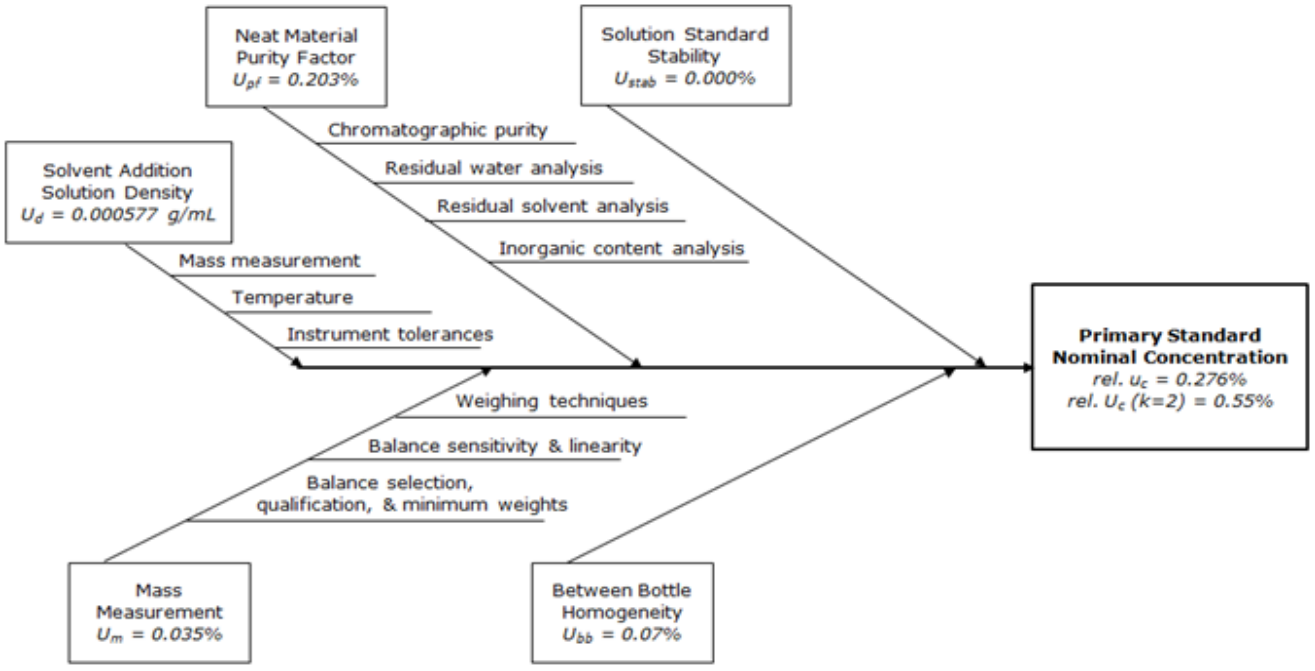
Packaging:	2 mL amber USP Type 1 glass ampoule containing not less than 1 mL of certified solution. Ampoules are overfilled to ensure a minimum of 1 mL volume can be transferred when using a 1mL Class A volumetric pipette.
Details on starting materials:	Each raw material utilized has been identified 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.



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Details on metrological traceability:

- This standard has been gravimetrically prepared using balances that have been fully qualified and calibrated to ISO 17025 requirements. All calibrations utilize NIST traceable weights which are calibrated externally by a qualified ISO 17025 accredited calibration laboratory to NIST standards. Qualification of each balance includes the assignment of a minimum weighing by a qualified and ISO 17025 accredited calibration vendor taking into consideration the balance and installed environmental conditions to ensure compliance with USP tolerances of NMT 0.10% relative error.
- Fill volume to predetermined specifications is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- The density and material Mass Balance Purity Factor of each raw material is traceable to the SI and higher order reference materials through mass measurement and instrument qualification and calibrations.

Details about certification process:

This standard has been prepared and certified under the ISO 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 Concentration (mg/mL)	**%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.

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Analyte Certification - Mass Balance Purity Factor

Each analyte is thoroughly identified and characterized using an orthogonal approach. A mass balance purity factor is assigned incorporating chromatographic purity and residual impurities. The mass balance purity factor and salt adjustment are utilized to calculate the weighing adjustment necessary to ensure accuracy of the solution standard concentration.

Material Name:	(±)-beta-Hydroxythiofentanyl HCl	**Molecular Weight (base):**	358.50
Material Lot:	FC10291802	**Molecular Weight (salt):**	394.96
Chemical Formula:	$C_{20}H_{26}N_2O_2S \bullet HCl$	**Salt Adjustment:**	1.102
CAS Number:	NA		

Material Characterization Summary

Analytical Test	**Method**	**Results**		
Primary Chromatographic Purity by HPLC/UV Analysis	SP10-0102	99.5% [1]		
Secondary Chromatographic Purity by GC/FID Analysis	SP10-0101	98.2%		
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 [2]	None Detected		
Residual Water Analysis by Karl Fischer Coulometry	AM1346 [2]	Below Quantitation Limit		
Inorganic Content by Microash Analysis	SP10-0135	< 0.2%		
Elemental Analysis	Outsourced		Calculated	Analyzed
		C	60.82%	60.77%
		H	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.

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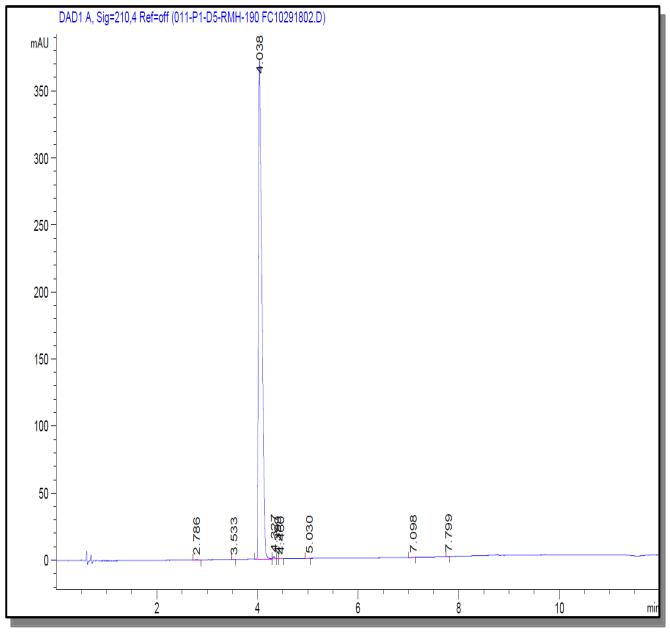
Spectral and Physical Data

HPLC/UV



Column: Ascentis Express Phenyl-Hexyl, 2.7 µm, 3.0 x 100 mm
Mobile Phase: A: Acetonitrile
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

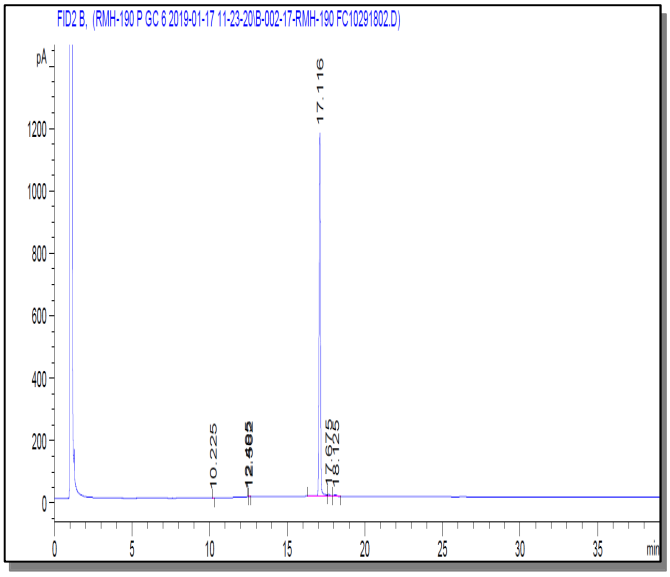
Flow Rate: 0.7 mL/min
Wavelength: 210 nm

Sample Name: FC10291802
Acquired: January 14, 2019

Peak #	Ret Time	Area %
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

GC/FID



Column: DB-35ms, 30 m x 0.53 mm ID, 1.0 µm film thickness
Temp Program: 60°C to 300°C at 20°C/min hold 27 min
Injector Temp: Cool-on-Column
Detector Temp: 325°C

Sample Name: FC10291802
Acquired: January 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

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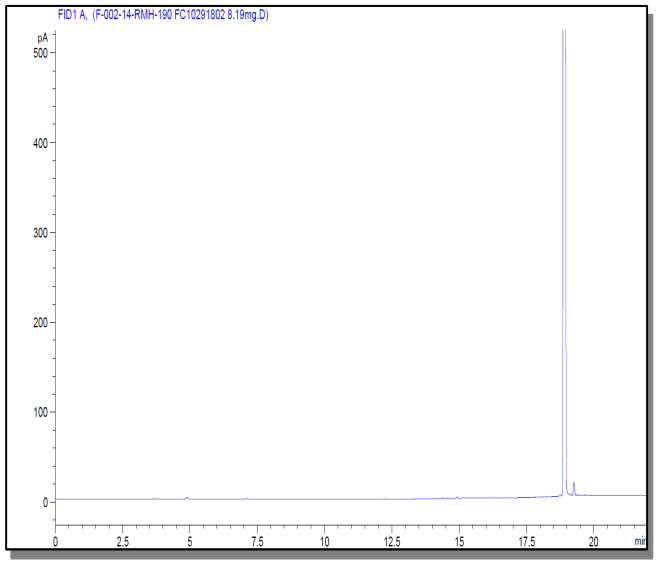
Spectral and Physical Data (cont.)

Residual Solvent Analysis by GC/FID Headspace



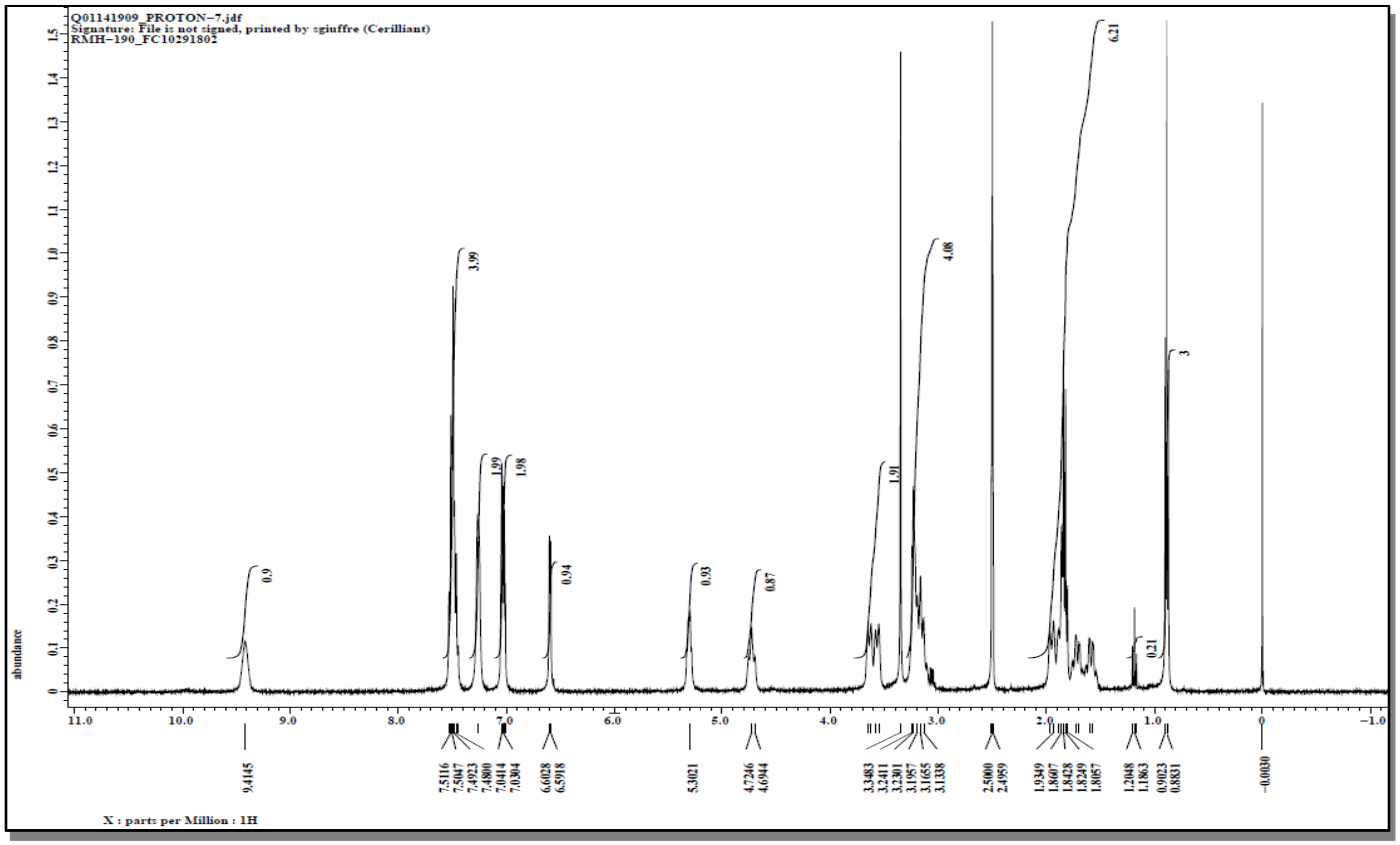
Column:	DB-ALC1 30 m x 0.53 mm, 3 µm film thickness
Temp Program:	40°C (12 min) to 220°C at 40°C/min (5.5 min)
Carrier Gas:	Helium
Flow Rate:	2.0 mL/min
Detector Heater Temp:	250°C
Injector:	Headspace Sampler
HS Oven Temp:	60°C
Vial Equilibration:	10 minutes
Sample Name:	FC10291802
Acquired:	January 15, 2019

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

ND - None Detected

^{1}H NMR

Instrument: JEOL ECS 400
Solvent: DMSO-D_6



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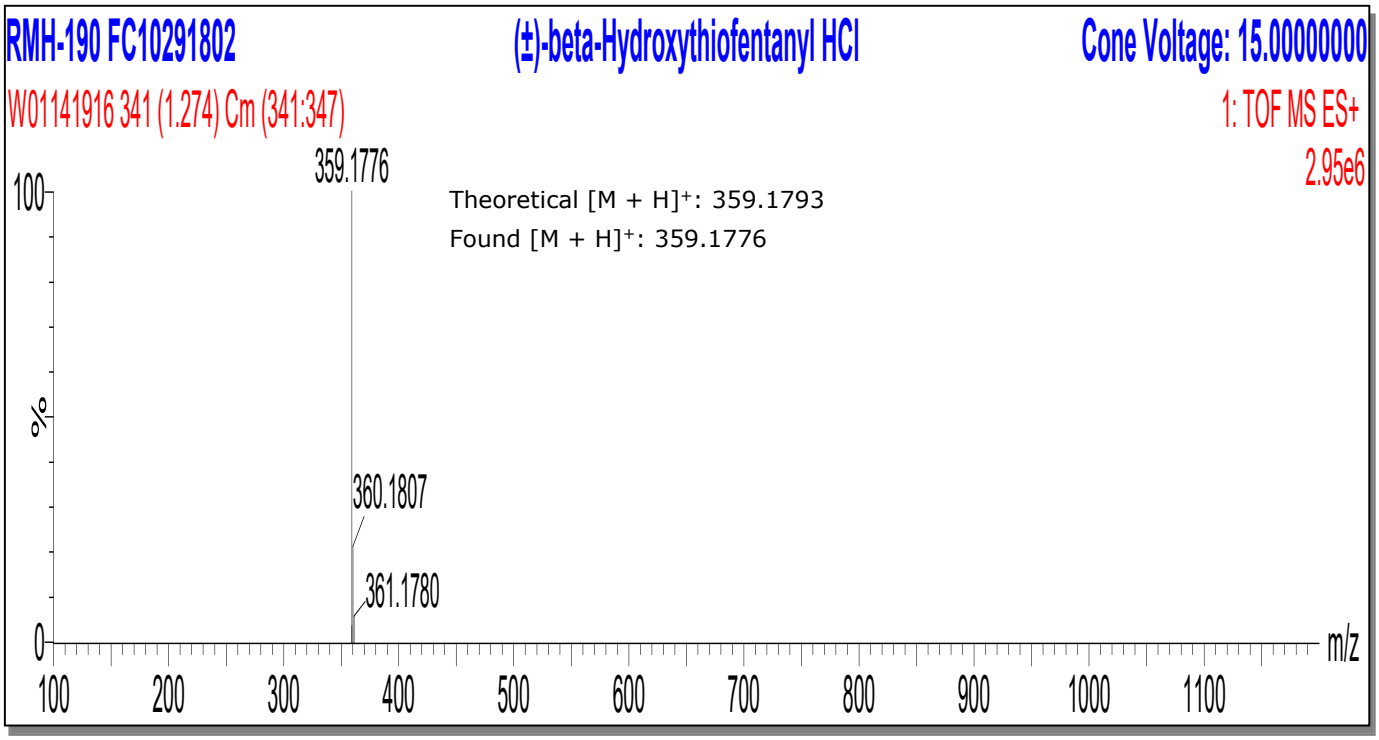
Spectral and Physical Data (cont.)

LC/MS

Column:	Ascentis Express C18, 2.7 µm, 3.0 x 50 mm	**Flow Rate:**	0.4 mL/min
Mobile Phase:	A: 0.1% Formic acid in Water	**Scan Range:**	100-1200 amu
	B: Acetonitrile	**Ionization:**	Electrospray, Positive Ion
Gradient:		**Instrument:**	Waters XEVO G2 QTOF
		Acquired:	January 14, 2019

Time (min)	% A	% B
0.0	80	20
0.5	80	20
4.0	20	80
5.8	20	80
6.0	80	20
8.0	80	20



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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 this product is listed below.*

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

Transport/Shipping: *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

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.
		Added Long Term Stability section.
02	December 15, 2020	Revised Retest Date from February 2021 to November 2021.

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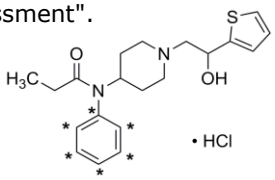
Certified Reference Material - Certificate of Analysis

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

(±)-N-[1-[2-Hydroxy-2-(2-thienyl)ethyl]-4-piperidinyl]-N-phenyl-propanamide-$^{13}C_6$ HCl

Product No.: H-138-1ML
Lot No.: FC12261809
Description of CRM: (±)-beta-Hydroxythiofentanyl-$^{13}C_6$ HCl in Methanol (Solution)
Nominal concentration is adjusted for HCl content.
Retest Date: November 2021 See Section "Stability Assessment".
Storage: Store unopened in freezer (-10 °C to -25 °C).
Shipping: Ambient See Section "Stability Assessment".
Chemical formula: $C_{14}{}^{13}C_6H_{26}N_2O_2S \bullet HCl$
CAS No.: NA
Regulatory: USDEA Schedule I

Cerilliant Quality
ISO 17034
ISO/IEC 17025
ISO 13485
ISO 14001
ISO 9001



Analyte	Certified Concentration ± associated uncertainty U, u=k*u (k=2)
(±)-beta-Hydroxythiofentanyl-$^{13}C_6$	**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 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.

Darron Ellsworth, Quality Assurance Manager

December 04, 2020
Issue Date

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

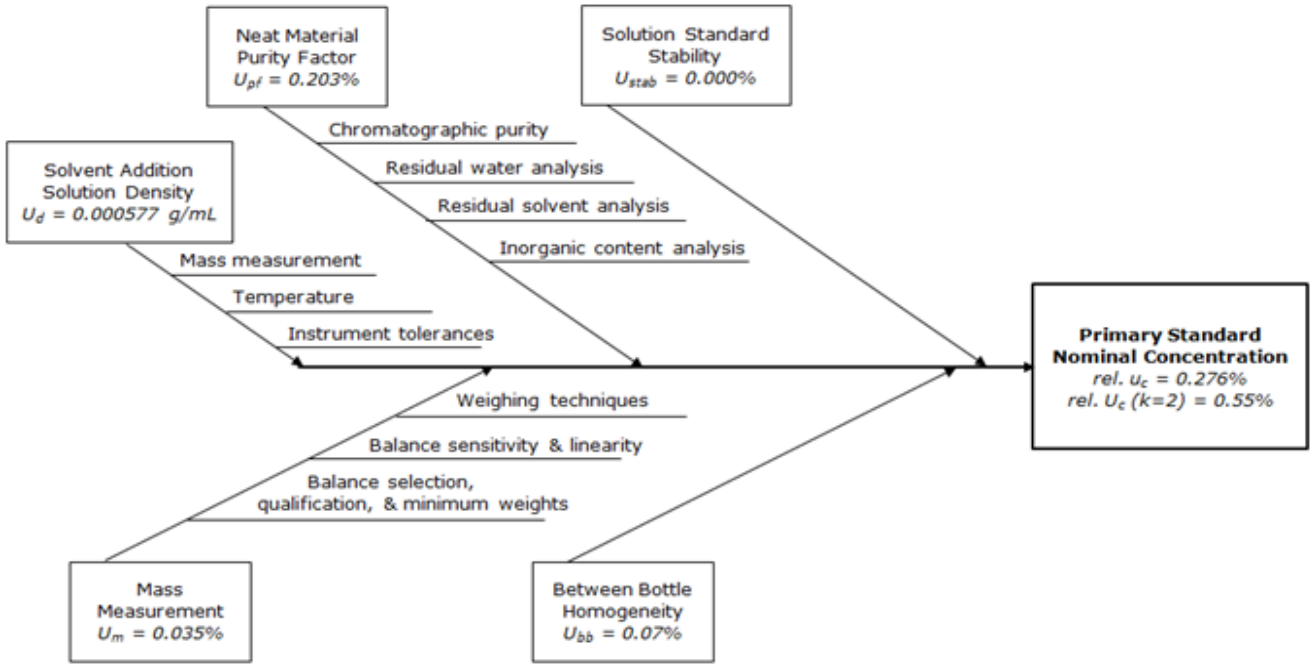
Packaging: 2 mL amber USP Type 1 glass ampoule containing not less than 1 mL of certified solution. Ampoules are overfilled to ensure a minimum of 1 mL volume can be transferred when using a 1mL Class A volumetric pipette.

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 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 (mg/mL)	**%RSD - Homogeneity**
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:	$C_{14}{}^{13}C_6H_{26}N_2O_2S$ • HCl	**Salt Adjustment:**	1.100
CAS Number:	NA		

Material Characterization Summary

Analytical Test	**Method**	**Results**		
Primary Chromatographic Purity by HPLC/UV Analysis	SP10-0102	98.7% [1]		
Secondary Chromatographic Purity by GC/FID Analysis	SP10-0101	98.9%		
Identity by LC/MS Analysis	SP10-0107	Consistent with Structure		
Isotopic Purity and Distribution by LC/MS SIM Analysis	SP10-0107	0.01% $^{13}C_0$ vs $^{13}C_6$		
		0.01% $^{13}C_0$	0.03% $^{13}C_4$	
		0.01% $^{13}C_1$	2.03% $^{13}C_5$	
		0.00% $^{13}C_2$	97.91% $^{13}C_6$	
		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 [2]	0.31%		
Residual Water Analysis by Karl Fischer Coulometry	AM1346 [2]	Below Quantitation Limit		
Inorganic Content by Microash Analysis	SP10-0135	< 0.2%		
Elemental Analysis	Outsourced		Calculated	Analyzed
		C	41.94%	59.77%
		H	6.79%	6.65%
		N	6.99%	7.08%
Mass Balance Purity Factor		98.40%		

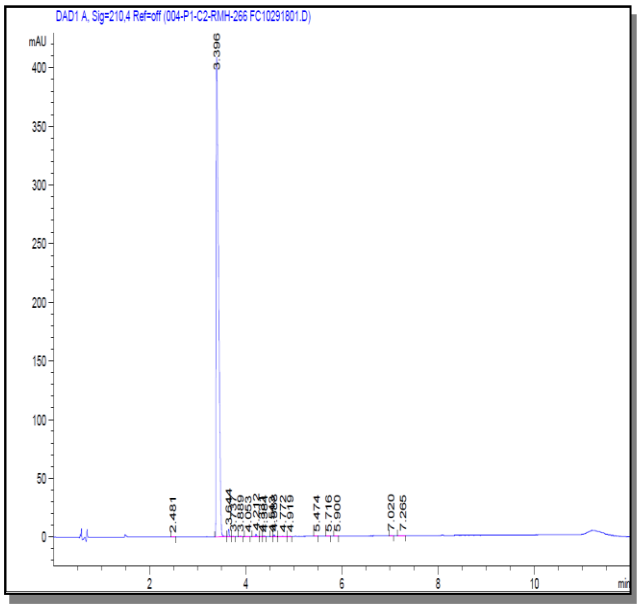
[1] 0.03% Norfentanyl-$^{13}C_6$ was detected by HPLC/UV analysis.

[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: Ascentis Express C18, 2.7 µm, 3.0 x 100 mm

Mobile Phase: A: Acetonitrile
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/min

Wavelength: 210 nm

Sample Name: FC10291801

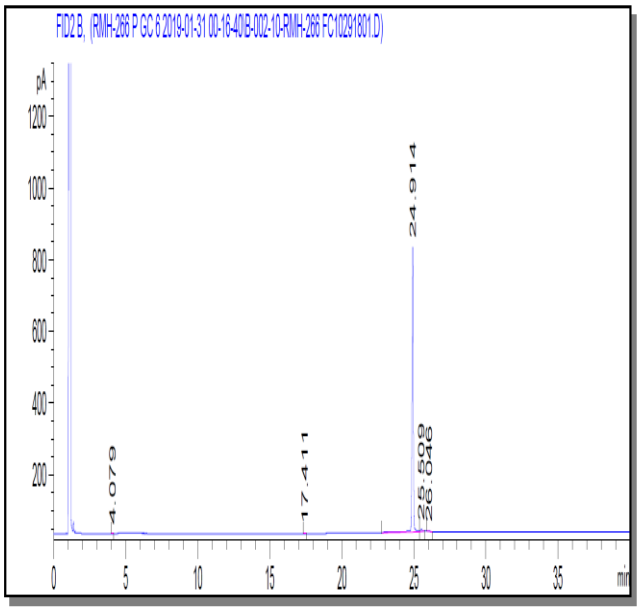
Acquired: February 06, 2019

Peak #	Ret Time	Area %
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-$^{13}C_6$.

Spectral and Physical Data (cont.)

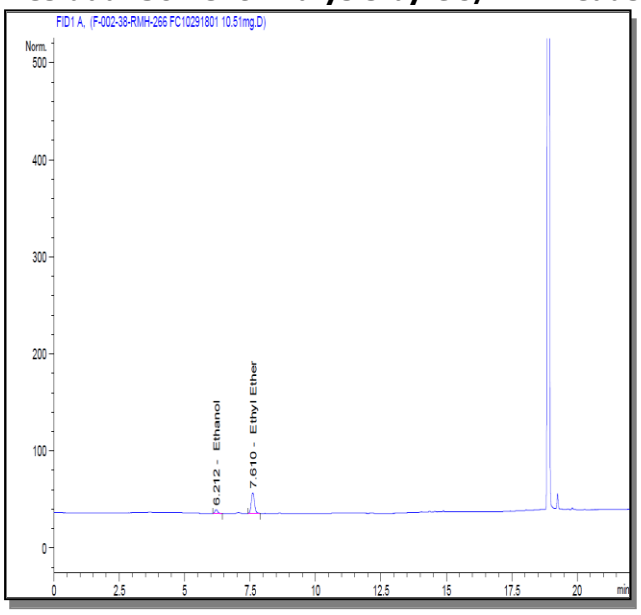
GC/FID



Column:	DB-35ms, 30 m x 0.53 mm ID, 1.0 µm film thickness
Temp Program:	40°C to 200°C at 40°C/min 200°C to 300°C at 5°C/min hold 16 min
Injector Temp:	Cool-on-Column
Detector Temp:	325°C
Sample Name:	FC10291801
Acquired:	January 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



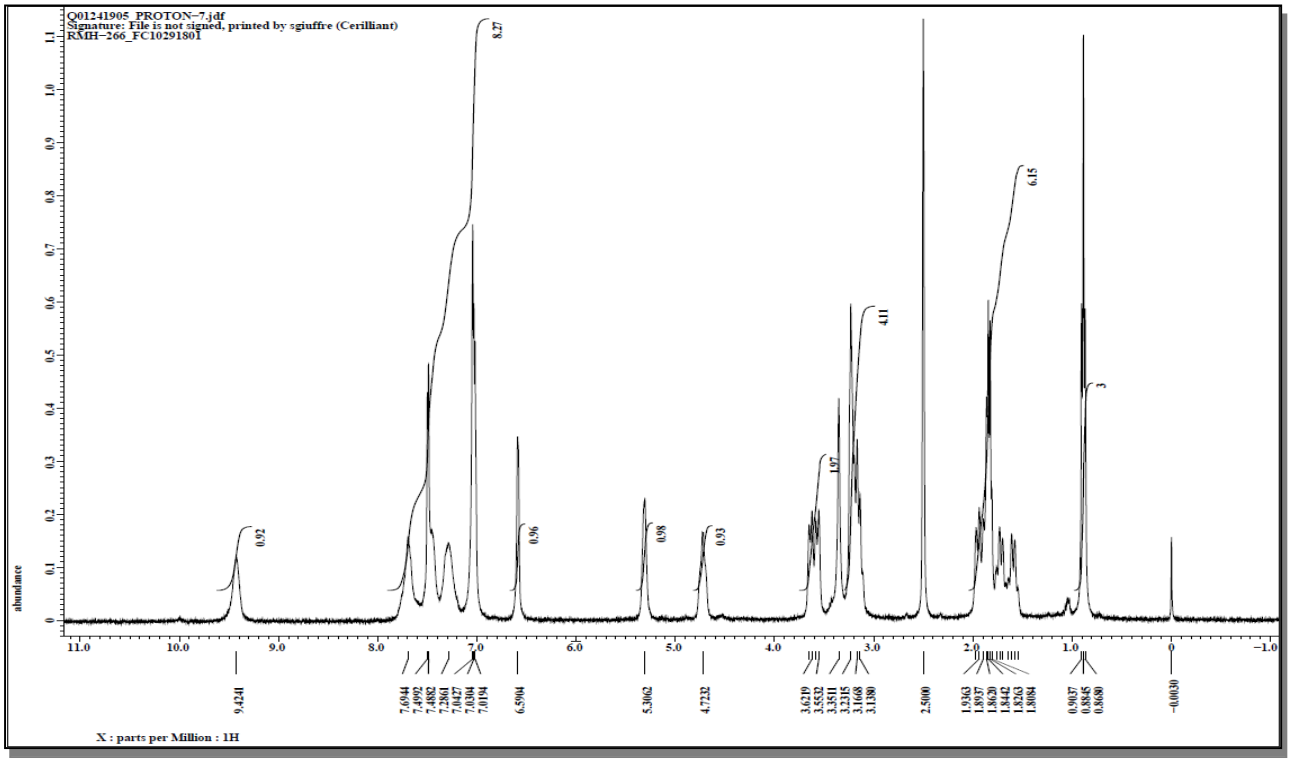
Column:	DB-ALC1 30 m x 0.53 mm, 3 µm film thickness
Temp Program:	40°C hold 12 min to 220°C at 40°C/min hold 5.5 min
Carrier Gas:	Helium
Flow Rate:	2.0 mL/min
Detector Heater Temp:	250°C
Injector:	Headspace Sampler
HS Oven Temp:	60°C
Vial Equilibration:	10 minutes
Sample Name:	FC10291801
Acquired:	January 23, 2019

Peak	Compound	Area	Weight %
1	Ethanol	28.36	0.24
2	Ethyl Ether	179.25	0.08
3	NMP	NA	NA
Total			**0.31**

Spectral and Physical Data (cont.)

^{1}H NMR

Instrument: JEOL ECS 400
Solvent: DMSO-D_6



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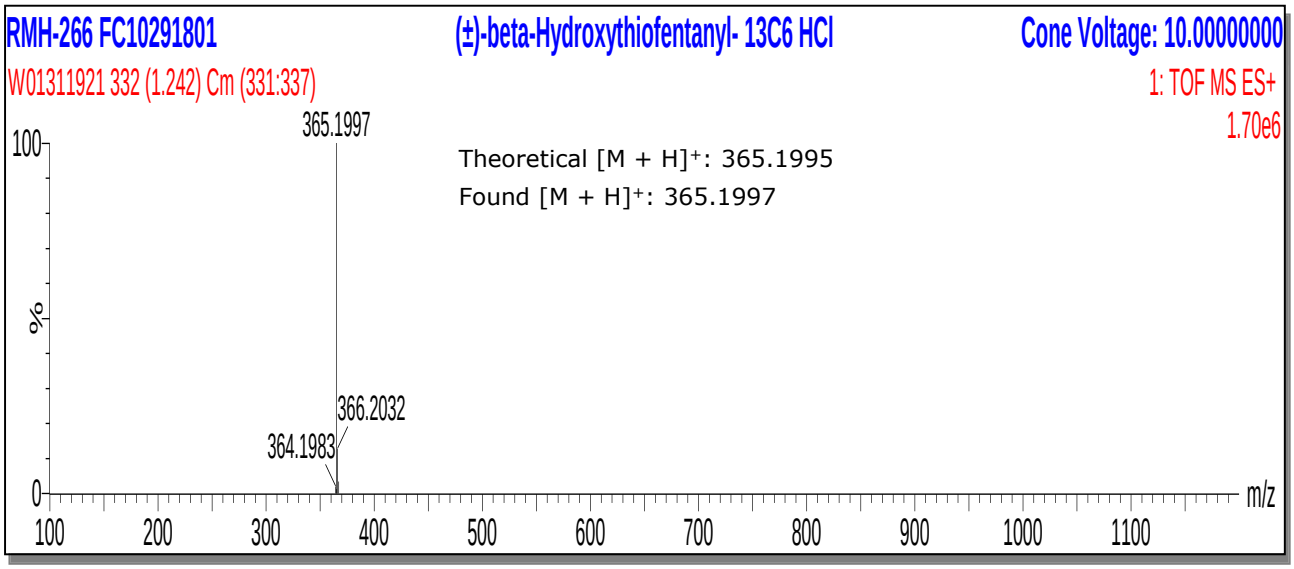
Spectral and Physical Data (cont.)

LC/MS

Column:	Ascentis Express C18, 2.7 µm, 3.0 x 50 mm	**Flow Rate:**	0.4 mL/min
Mobile Phase:	A: 0.1% Formic acid in Water B: Acetonitrile	**Scan Range:**	100-1200 amu
		Ionization:	Electrospray, Positive Ion
		Instrument:	Waters XEVO G2 QTOF
Gradient:		**Acquired:**	January 31, 2019

Time (min)	% A	% B
0.0	80	20
0.5	80	20
4.0	20	80
5.8	20	80
6.0	80	20
8.0	80	20



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Spectral and Physical Data (cont.)

Isotopic Purity by LC/MS

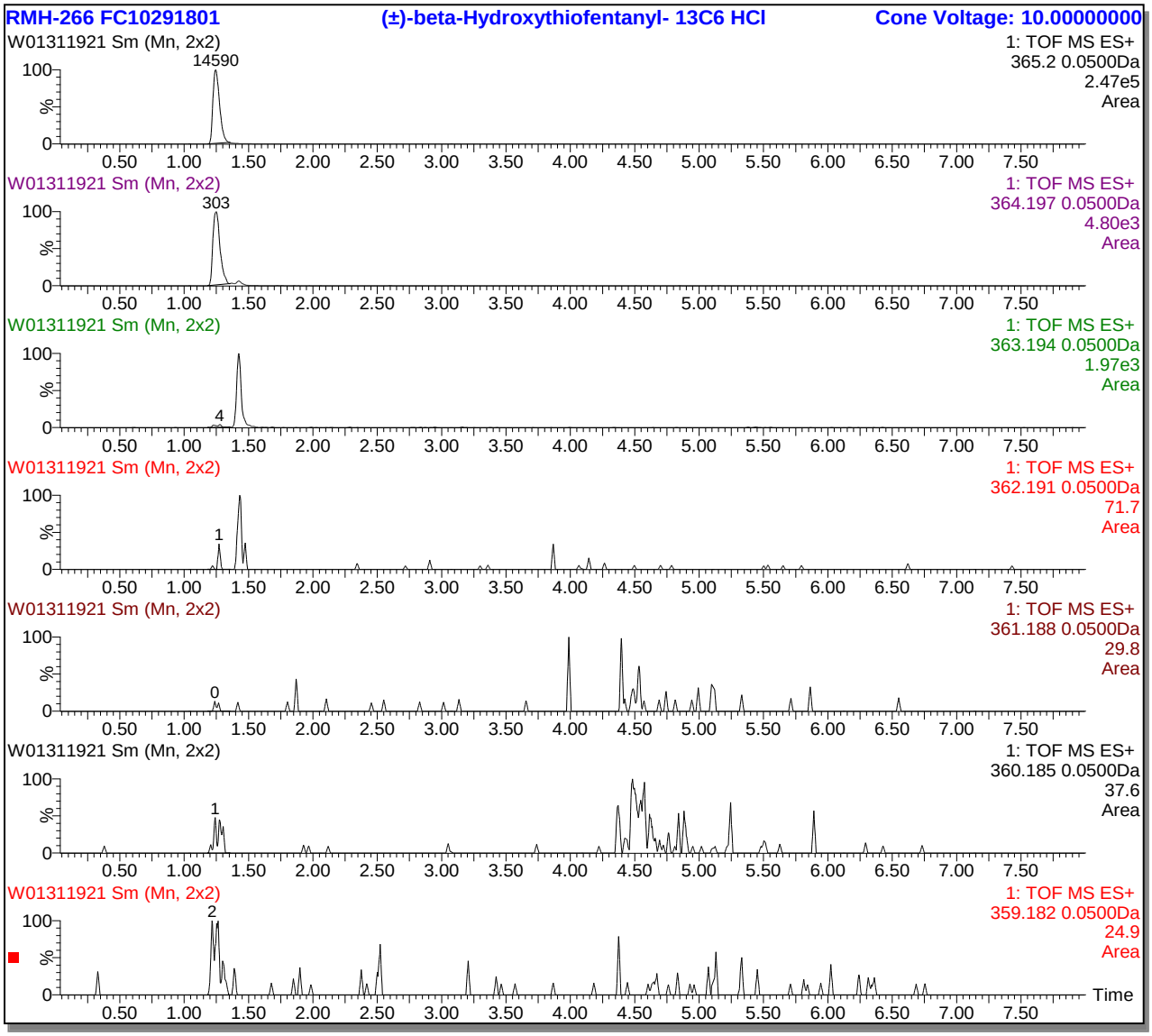
Column: Ascentis Express C18, 2.7 µm, 3.0 x 50 mm

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

Gradient:

Time (min)	% A	% B
0.0	80	20
0.5	80	20
4.0	20	80
5.8	20	80
6.0	80	20
8.0	80	20

Flow Rate: 0.4 mL/min
Scan Range: 359-365 amu
Ionization: Electrospray, Positive Ion
Instrument: Waters XEVO G2 QTOF
Acquired: January 31, 2019



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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 (H-130-0.5ML, (±)-beta-Hydroxythiofentanyl HCl) is listed below.*

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

Transport/Shipping: *Stability studies support the transport of this product at ambient conditions.*

Long Term Stability: *Long term stability has been assessed for Freezer storage (-10 °C to -25 °C) conditions. Stability of a minimum of 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	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.

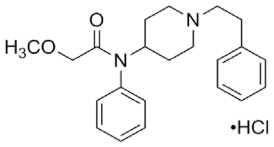
Certified Reference Material - Certificate of Analysis

Methoxyacetyl fentanyl , Primary Measurement Standard

2-Methoxy-N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl] acetamine HCl

Cerilliant Quality
ISO 17034
ISO/IEC 17025
ISO 13485
ISO 14001
ISO 9001

Product No.: M-220-1ML
Lot No.: FC01031901
Description of CRM: Methoxyacetyl fentanyl HCl in Methanol (Solution)
Nominal concentration is adjusted for HCl content.
Retest Date: December 2021 See Section "Stability Assessment".
Storage: Store unopened in freezer (-10 °C to -25 °C).
Shipping: Ambient. See Section "Stability Assessment".
Chemical formula: $C_{22}H_{28}N_2O_2 \bullet HCl$
CAS No.: 101365-54-2
Regulatory: USDEA Schedule I



Analyte	Certified Concentration ± 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 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

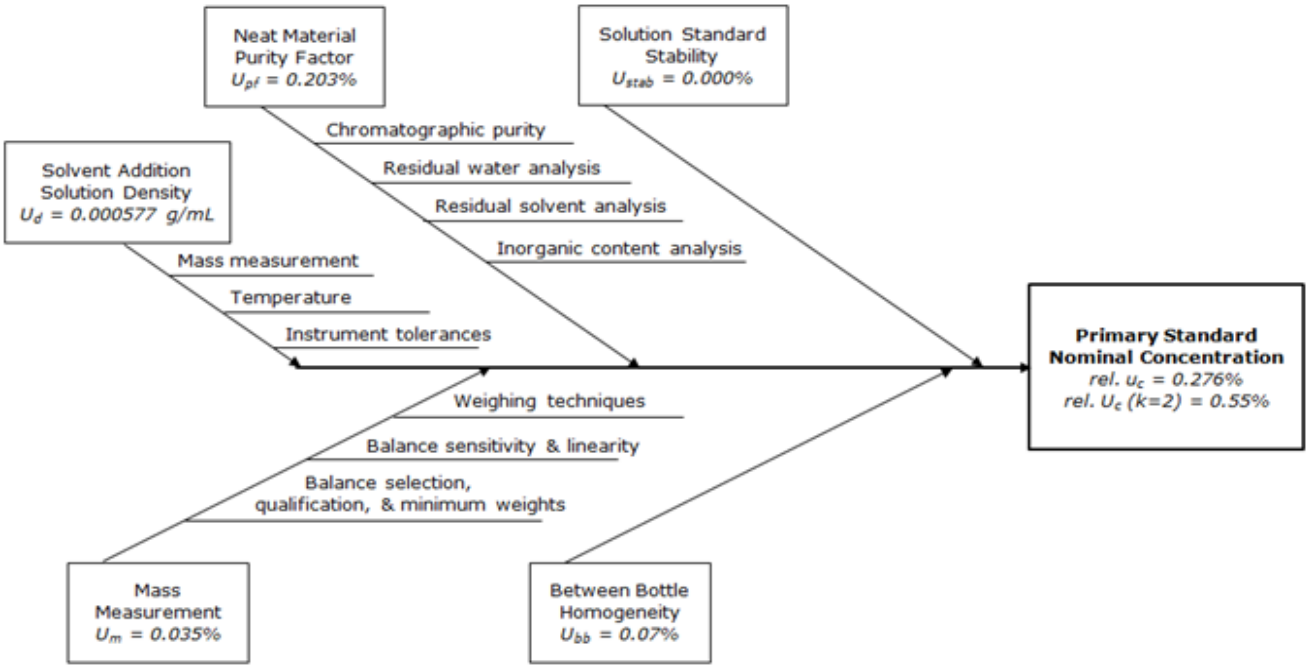
December 30, 2020
Issue Date

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.



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Details on metrological traceability:

- This standard has been gravimetrically prepared using balances that have been fully qualified and calibrated to ISO 17025 requirements. All calibrations utilize NIST traceable weights which are calibrated externally by a qualified ISO 17025 accredited calibration laboratory to NIST standards. Qualification of each balance includes the assignment of a minimum weighing by a qualified and ISO 17025 accredited calibration vendor taking into consideration the balance and installed environmental conditions to ensure compliance with USP tolerances of NMT 0.10% relative error.
- Fill volume to predetermined specifications is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- The density and material Mass Balance Purity Factor of each raw material is traceable to the SI and higher order reference materials through mass measurement and instrument qualification and calibrations.

Details about certification process:

This standard has been prepared and certified under the ISO 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:	1.5 mL/min		
Wavelength:	210 nm		

		Verified Concentration (mg/mL)	**%RSD - Homogeneity**
Standard Solution	**Lot Number**	**Actual Results**	**Actual Results**
New Lot	FC01031901	0.996	0.7

- Concentration is verified through multiple analyses and is calculated as the average of multiple analyses compared to an independently prepared calibration solution.
- Within-sample and between-sample homogeneity of the New Lot is ensured through rigorous production process controls statistically analyzed to evaluate risk and verified by analysis. Multiple samples pulled from across the lot using a random stratified sampling plan were analyzed to verify homogeneity. % RSD results shown above for the New Lot demonstrate ampoule-to-ampoule homogeneity.

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Analyte Certification - Mass Balance Purity Factor

Each analyte is thoroughly identified and characterized using an orthogonal approach. A mass balance purity factor is assigned incorporating chromatographic purity and residual impurities. The mass balance purity factor and salt adjustment are utilized to calculate the weighing adjustment necessary to ensure accuracy of the solution standard concentration.

Material Name:	Methoxyacetyl fentanyl HCl	**Molecular Weight (base):**	352.47
Material Lot:	FC10161802	**Molecular Weight (salt):**	388.93
Chemical Formula:	$C_{22}H_{28}N_2O_2$ • HCl	**Salt Adjustment:**	1.103
CAS Number:	101365-54-2		

Material Characterization 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.

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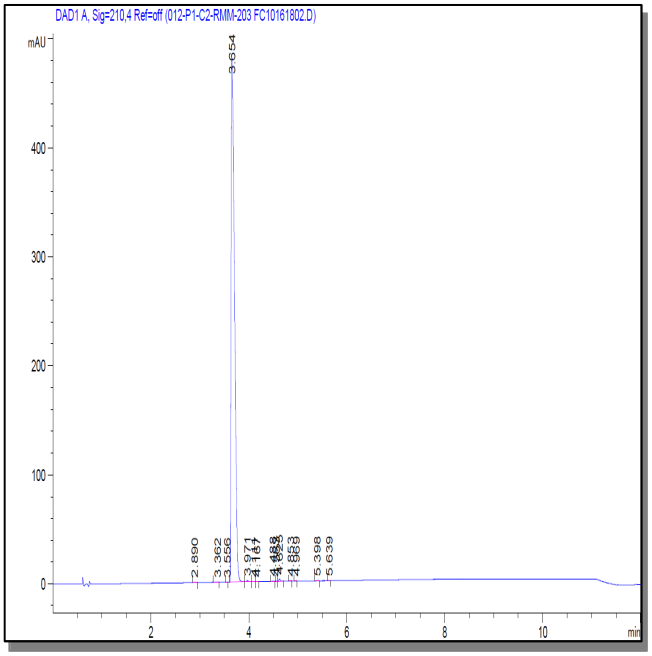
Spectral and Physical Data

HPLC/UV



Column: Ascentis Express Phenyl-Hexyl, 2.7 µm, 3.0 x 100 mm

Mobile Phase: A: Acetonitrile
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/min

Wavelength: 210 nm

Sample Name: FC10161802

Acquired: February 07, 2019

Peak #	Ret Time	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
7	4.17	0.02
8	4.49	0.04
9	4.56	0.01
10	4.63	0.20
11	4.85	0.00
12	4.97	0.01
13	5.40	0.03
14	5.64	0.01

Peak 5 has been identified as 4-ANPP

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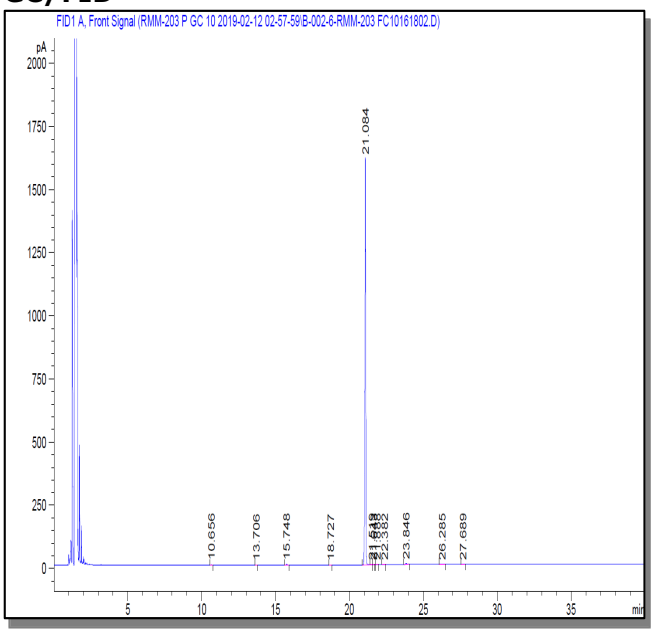
Spectral and Physical Data (cont.)

GC/FID



Column: DB-5ms, 30 m x 0.53 mm ID, 1.5 µm film thickness

Temp Program: 40°C to 200°C at 40°C/min
200°C to 300°C at 5°C/min hold 16 min

Injector Temp: Cool-on-Column

Detector Temp: 325°C

Sample Name: FC10161802

Acquired: February 12, 2019

Peak #	Ret 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

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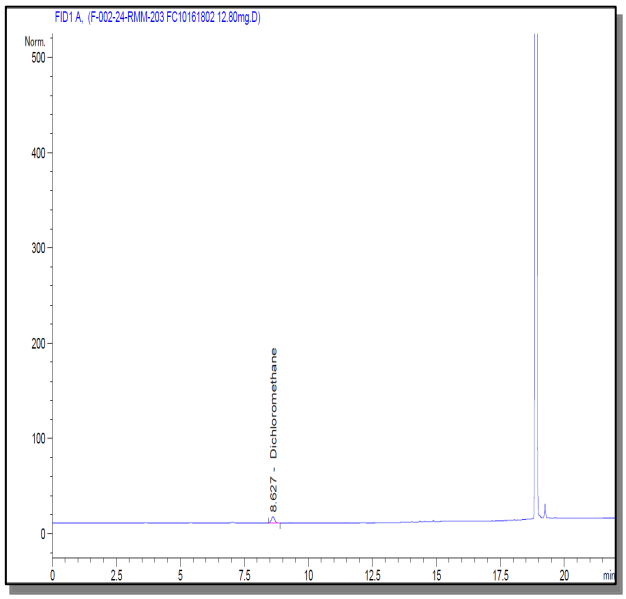
Spectral and Physical Data (cont.)

Residual Solvent Analysis by GC/FID Headspace

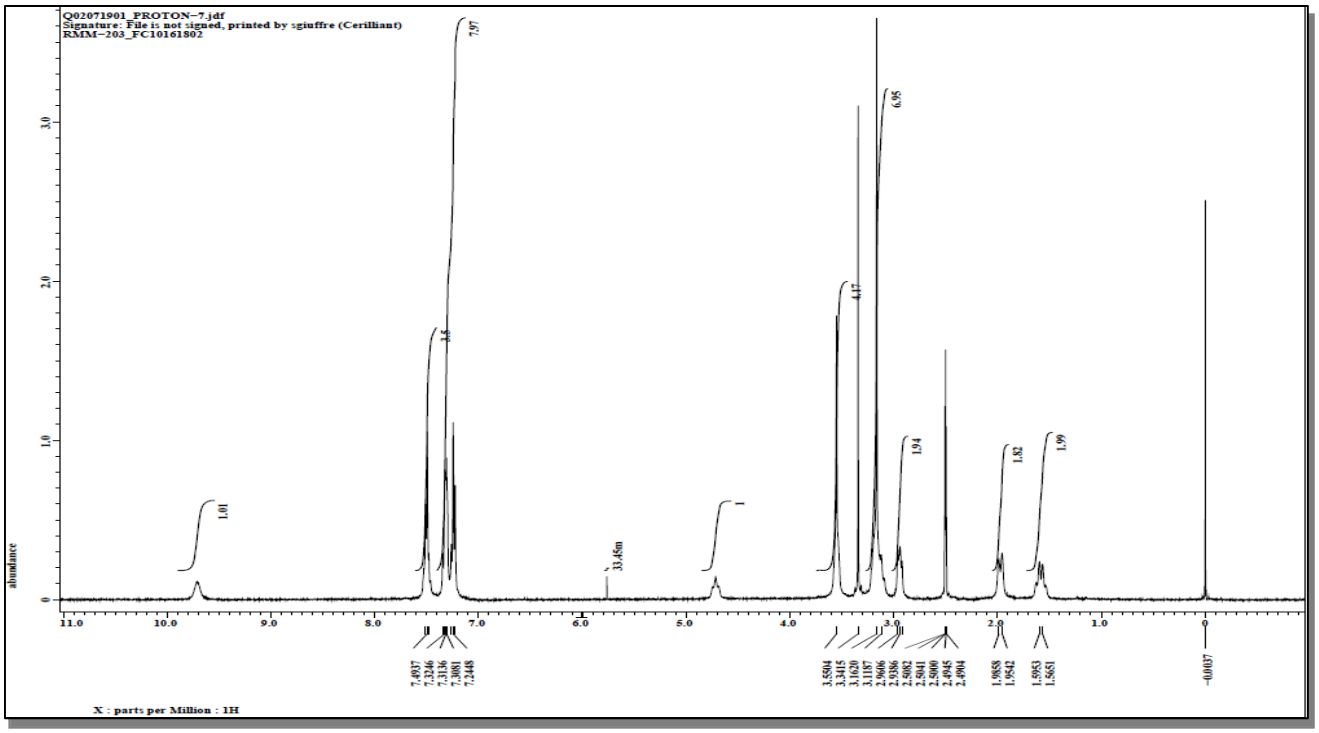


Column:	DB-ALC1 30 m x 0.53 mm, 3 µm film thickness
Temp Program:	40°C hold 12 min to 220°C at 40°C/min hold 5.5 min
Carrier Gas:	Helium
Flow Rate:	2.0 mL/min
Detector Heater Temp:	250°C
Injector:	Headspace Sampler
HS Oven Temp:	60°C
Vial Equilibration:	10 minutes
Sample Name:	FC10161802
Acquired:	February 14, 2019

Peak	Compound	Area	Weight %
1	Dichloromethane	57.13	0.53
2	NMP	NA	NA
Total			**0.53**

^{1}H NMR

Instrument:	JEOL ECS 400
Solvent:	DMSO-D_6



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Spectral and Physical Data (cont.)

LC/MS

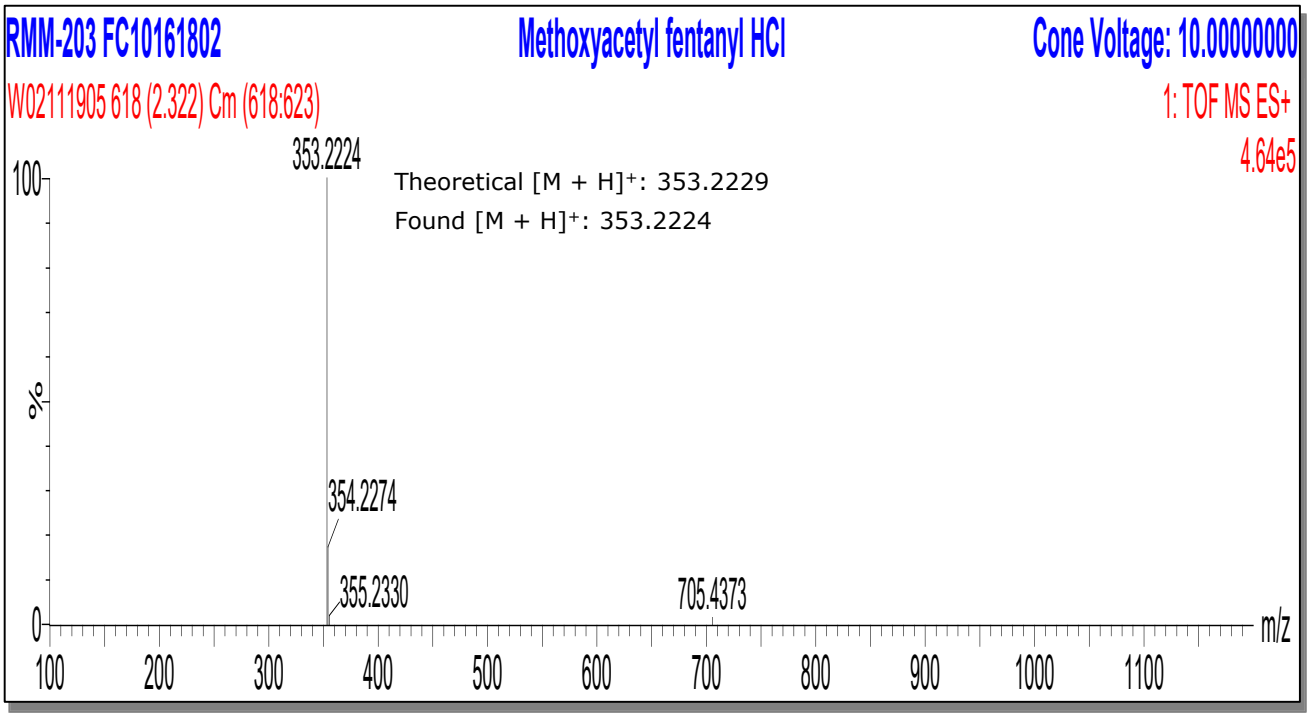
Column: Ascentis Express C18, 2.7 µm, 3.0 x 50 mm

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

Gradient:

Time (min)	% A	% B
0.0	90	10
0.5	90	10
4.0	50	50
5.8	50	50
6.0	90	10
8.0	90	10

Flow Rate: 0.4 mL/min
Scan Range: 100-1200 amu
Ionization: Electrospray, Positive Ion
Instrument: Waters XEVO G2 QTOF
Acquired: February 11, 2019



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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 this product is listed below.*

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

Transport/Shipping: *Stability studies support the transport of this product at ambient conditions.*

Long Term Stability: *Long term stability has been assessed for Freezer storage (-10 °C to -25 °C) conditions. Stability of a minimum of 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 29, 2020	Revised Retest Date May 2020 to March 2021.
		Added Long Term Stability Section.
02	December 30, 2020	Revised Retest Date March 2021 to December 2021.

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

Certified Reference Material - Certificate of Analysis

Methoxyacetyl fentanyl-$^{13}C_6$, Primary Measurement Standard

2-Methoxy-N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl] acetamine-$^{13}C_6$ HCl

Cerilliant Quality
ISO 17034
ISO/IEC 17025
ISO 13485
ISO 14001
ISO 9001

Product No.: M-221-1ML

Lot No.: FC01141901

Description of CRM: Methoxyacetyl fentanyl-$^{13}C_6$ HCl in Methanol (Solution)
Nominal concentration is adjusted for HCl content.

Retest Date: December 2021 See Section "Stability Assessment".

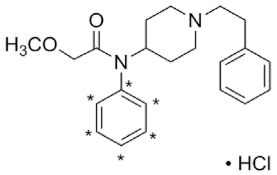
Storage: Store unopened in freezer (-10 °C to -25 °C).

Shipping: Ambient. See Section "Stability Assessment".

Chemical formula: $C_{16}{}^{13}C_6H_{28}N_2O_2$ • HCl

CAS No.: NA

Regulatory: USDEA Schedule I



Analyte	Certified Concentration ± associated uncertainty U, u=k*u (k=2)
Methoxyacetyl 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.

Darron Ellsworth, Quality Assurance Manager

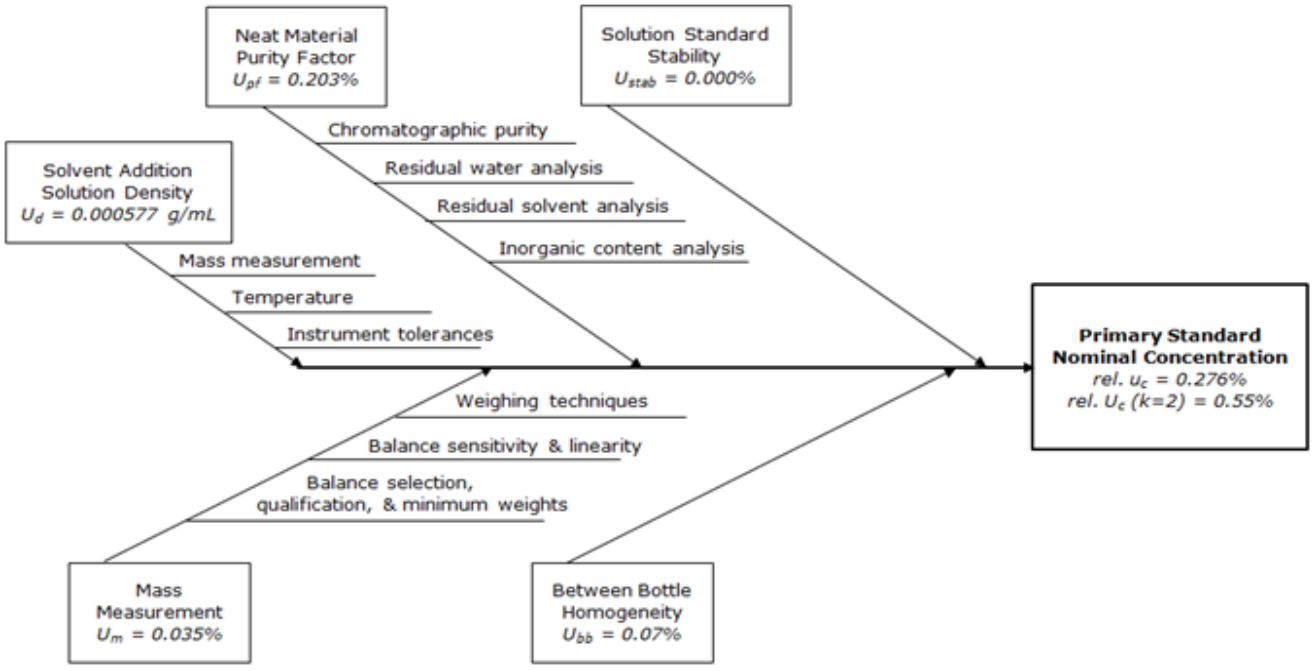
December 30, 2020
Issue Date

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.



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Details on metrological traceability:

- This standard has been gravimetrically prepared using balances that have been fully qualified and calibrated to ISO 17025 requirements. All calibrations utilize NIST traceable weights which are calibrated externally by a qualified ISO 17025 accredited calibration laboratory to NIST standards. Qualification of each balance includes the assignment of a minimum weighing by a qualified and ISO 17025 accredited calibration vendor taking into consideration the balance and installed environmental conditions to ensure compliance with USP tolerances of NMT 0.10% relative error.
- Fill volume to predetermined specifications is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- The density and material Mass Balance Purity Factor of each raw material is traceable to the SI and higher order reference materials through mass measurement and instrument qualification and calibrations.

Details about certification process:

This standard has been prepared and certified under the ISO 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 (mg/mL)	**%RSD - Homogeneity**
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.

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Analyte Certification - Mass Balance Purity Factor

Each analyte is thoroughly identified and characterized using an orthogonal approach. A mass balance purity factor is assigned incorporating chromatographic purity and residual impurities. The mass balance purity factor and salt adjustment are utilized to calculate the weighing adjustment necessary to ensure accuracy of the solution standard concentration.

Material Name:	Methoxyacetyl fentanyl-$^{13}C_6$ HCl	**Molecular Weight (base):**	358.43
Material Lot:	FC10311801	**Molecular Weight (salt):**	394.89
Chemical Formula:	$C_{16}{}^{13}C_6H_{28}N_2O_2$ • HCl	**Salt Adjustment:**	1.102
CAS Number:	NA		

Material Characterization Summary

Analytical Test	**Method**	**Results**	
Primary Chromatographic Purity by HPLC/UV Analysis	SP10-0102	99.6%	
Secondary Chromatographic Purity by GC/FID Analysis	SP10-0101	99.8%	
Identity by LC/MS Analysis	SP10-0107	Consistent with Structure	
Isotopic Purity and Distribution by LC/MS SIM Analysis	SP10-0107	0.00% $^{13}C_0$ vs $^{13}C_6$	
		0.00% $^{13}C_0$	0.08% $^{13}C_4$
		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 Analysis	USP <761>, SP10-0116	Consistent with Structure	
Residual Solvent Analysis by GC/FID Headspace	AM1087 [1]	0.14%	
Residual Water Analysis by Karl Fischer Coulometry	AM1346 [1]	Below Quantitation Limit	
Inorganic Content by Microash Analysis	SP10-0135	< 0.2%	
Mass Balance Purity Factor		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.

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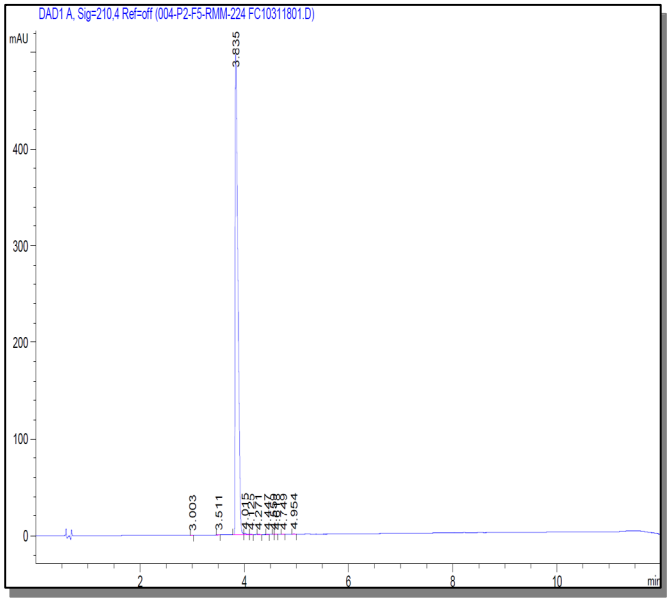
Spectral and Physical Data

HPLC/UV



Column: Ascentis Express C18, 2.7 µm, 3.0 x 100 mm

Mobile Phase: A: Acetonitrile
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/min

Wavelength: 210 nm

Sample Name: FC10311801

Acquired: 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
10	4.75	0.02
11	4.95	0.05

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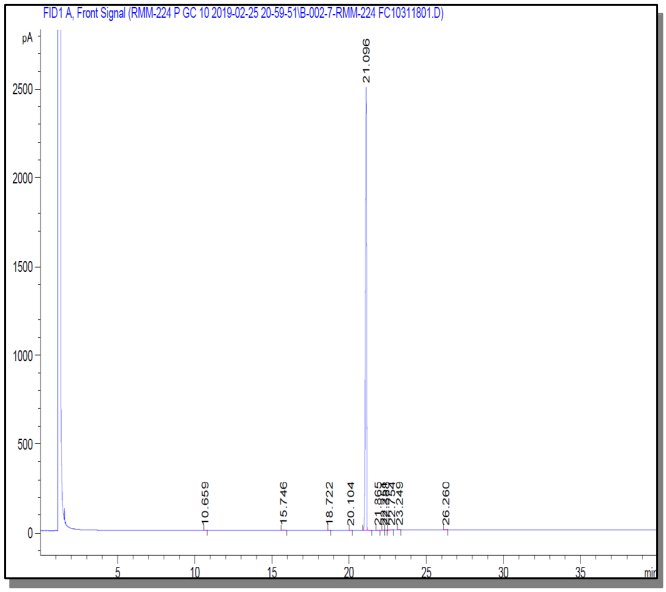
Spectral and Physical Data (cont.)

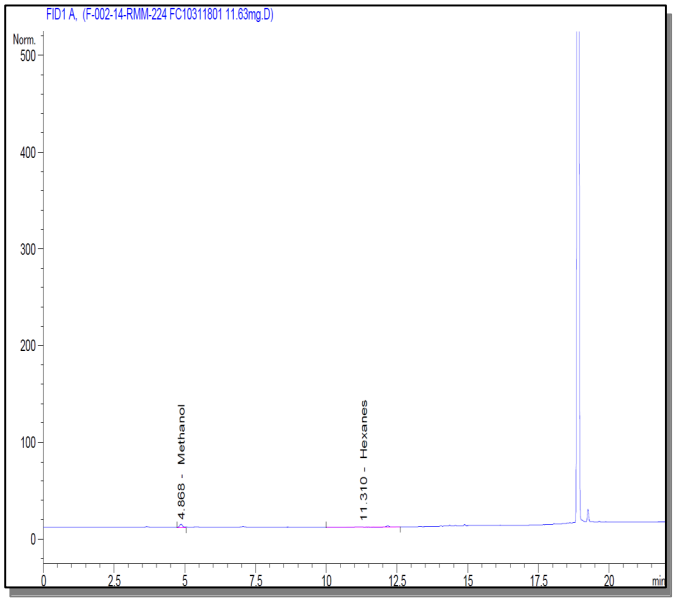
GC/FID



Column:	DB-5ms, 30 m x 0.53 mm ID, 1.5 µm film thickness
Temp Program:	40°C to 200°C at 40°C/min 200°C to 300°C at 5°C/min hold 16 min
Injector Temp:	Cool-on-Column
Detector Temp:	325°C
Sample Name:	FC10311801
Acquired:	February 25, 2019

Peak #	Ret Time	Area %
1	10.66	0.02
2	15.75	0.10
3	18.72	0.01
4	20.10	0.01
5	21.10	99.76
6	21.87	0.02
7	22.25	0.01
8	22.39	0.01
9	22.75	0.02
10	23.25	0.04
11	26.26	0.01

Residual Solvent Analysis by GC/FID Headspace



Column:	DB-ALC1 30 m x 0.53 mm, 3 µm film thickness
Temp Program:	40°C hold 12 min to 220°C at 40°C/min hold 5.5 min
Carrier Gas:	Helium
Flow Rate:	2.0 mL/min
Detector Heater Temp:	250°C
Injector:	Headspace Sampler
HS Oven Temp:	60°C
Vial Equilibration:	10 minutes
Sample Name:	FC10311801
Acquired:	February 26, 2019

Peak	Compound	Area	Weight %
1	Methanol	19.17	0.14
2	Hexanes	6.31	BQL
3	NMP	NA	NA
Total			**0.14**

BQL - Below Quantitation Limit

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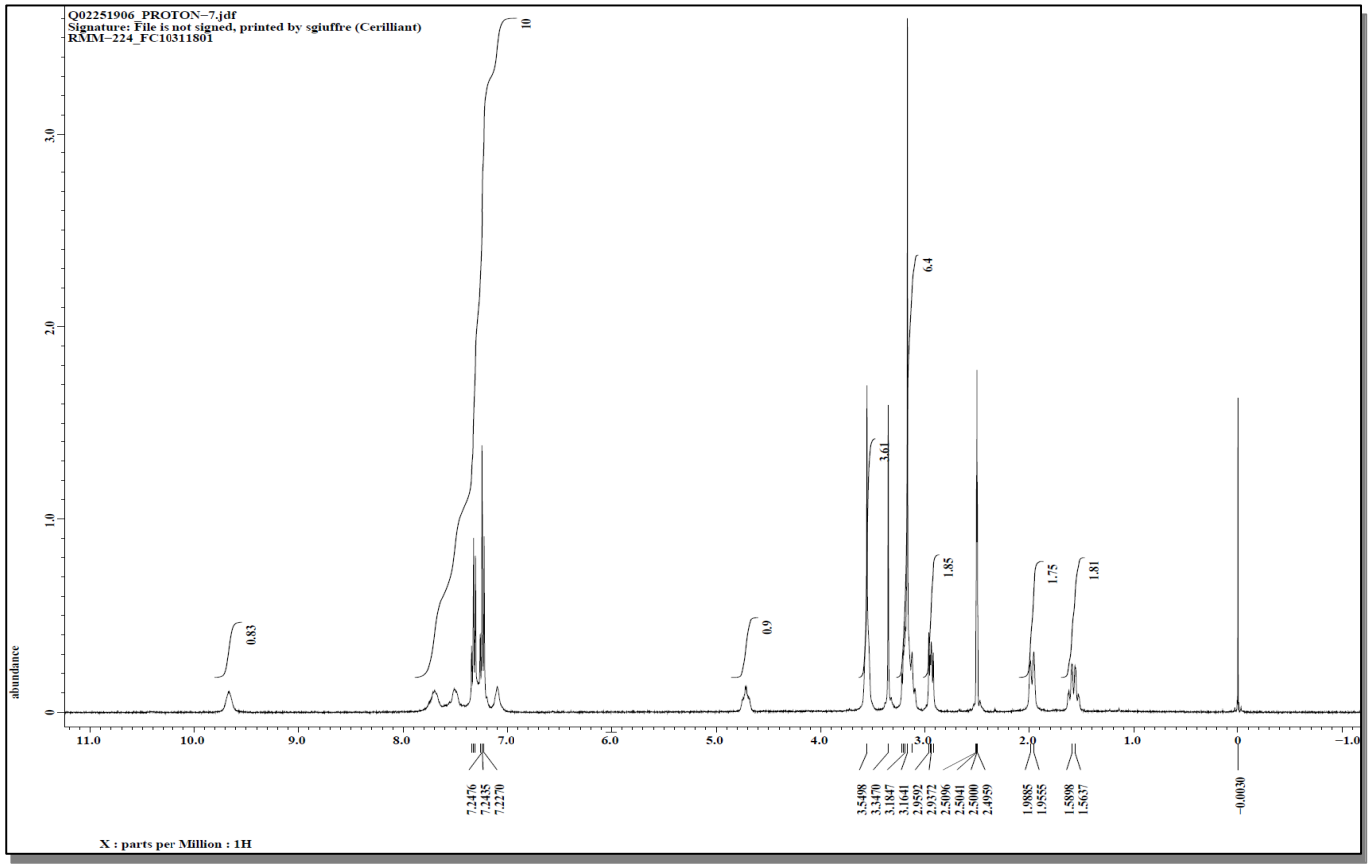
Spectral and Physical Data (cont.)

^{1}H NMR

Instrument: JEOL ECS 400
Solvent: DMSO-D_6



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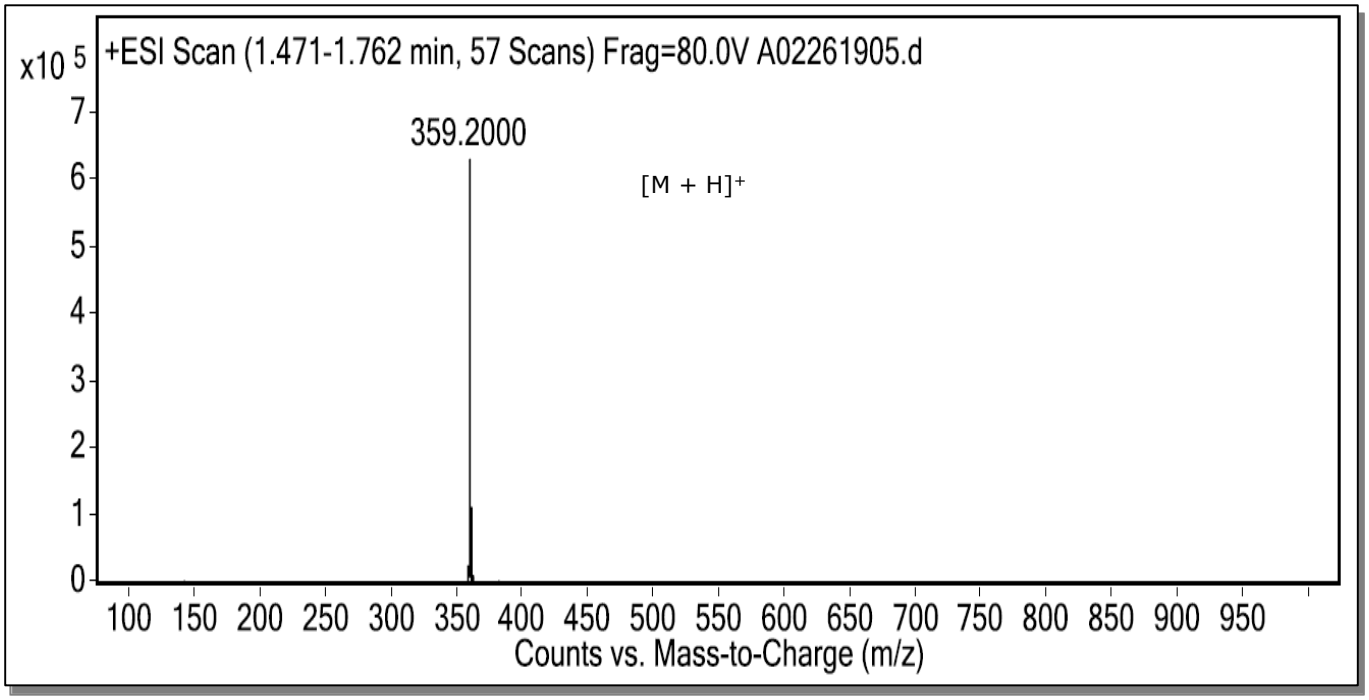
Spectral and Physical Data (cont.)

LC/MS

Column: Kinetex C18, 2.6 µm, 2.1 x 50 mm
Mobile Phase: A: 0.1% Formic acid in Water
B: Acetonitrile
Gradient:

Time (min)	% A	% B
0.0	80	20
5.0	20	80
6.0	20	80
7.0	80	20
11.0	80	20

Flow Rate: 0.5 mL/min
Scan Range: 100-1000 amu
Ionization: Electrospray, Positive Ion
Instrument: Agilent 6410A Mass Spectrometer
Acquired: February 26, 2019



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Spectral and Physical Data (cont.)

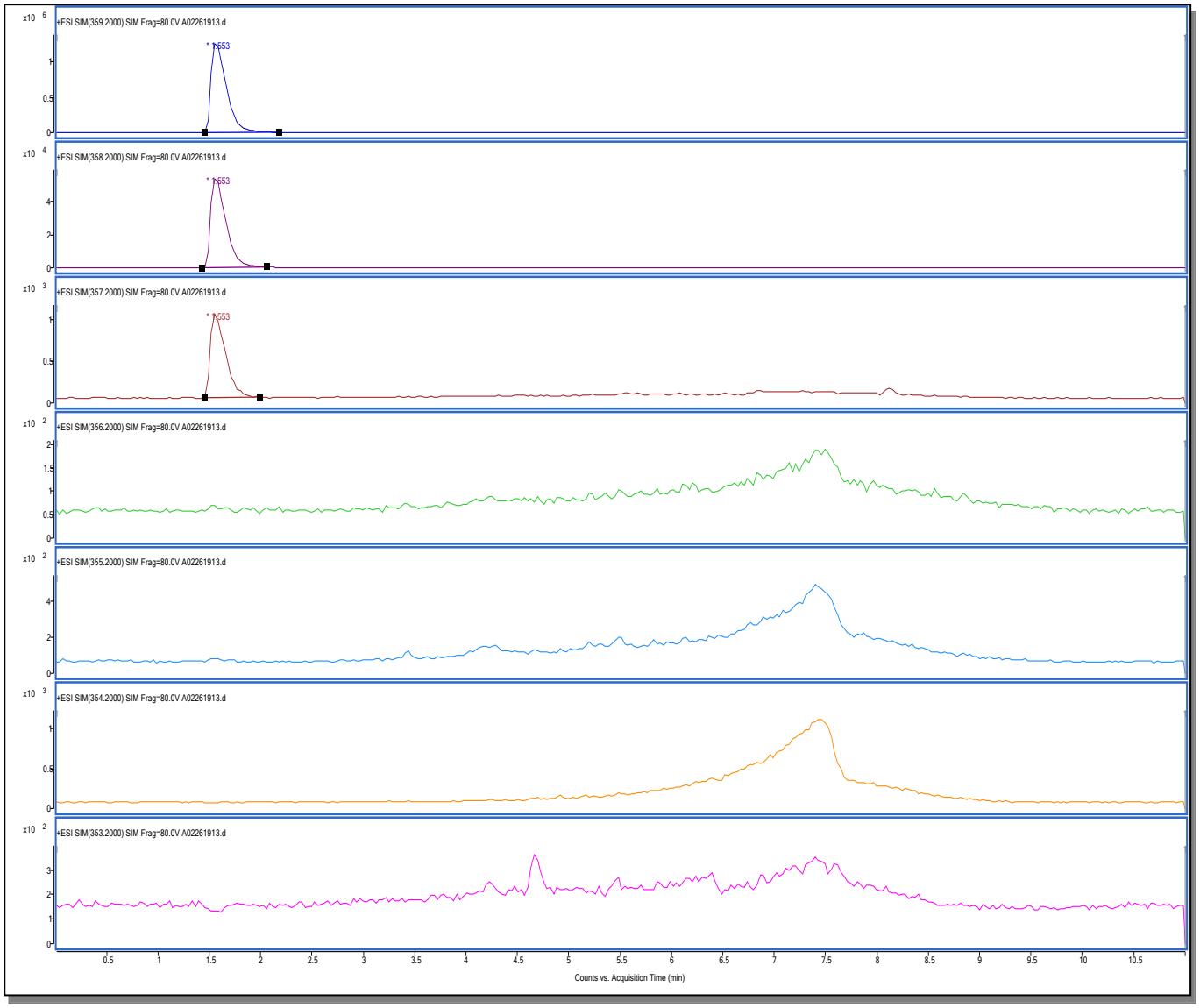
Isotopic Purity by LC/MS SIM

Column: Kinetex C18, 2.6 µm, 2.1 x 50 mm
Mobile Phase: A: 0.1% Formic acid in Water
B: Acetonitrile

Gradient:

Time (min)	% A	% B
0.0	80	20
5.0	20	80
6.0	20	80
7.0	80	20
11.0	80	20

Flow Rate: 0.5 mL/min
Scan Range: 353-359 amu
Ionization: Electrospray, Positive Ion
Instrument: Agilent 6410A Mass Spectrometer
Acquired: February 26, 2019



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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 (M-200-0.5ML, Methoxyacetyl fentanyl HCl) is listed below.*

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

Transport/Shipping: *Stability studies support the transport of this product at ambient conditions.*

Long Term Stability: *Long term stability has been assessed for Freezer storage (-10 °C to -25 °C) conditions. Stability of a minimum of 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 22, 2019	Initial version.
01	April 02, 2019	Revised Chemical Name Synonym.
02	April 29, 2020	Revised Retest Date from May 2020 to March 2021.
		Added Long Term Stability.
03	December 30, 2020	Revised Retest Date from March 2021 to December 2021.

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

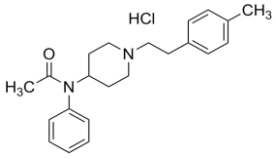
Certified Reference Material - Certificate of Analysis

4'-Methyl acetyl fentanyl, Primary Measurement Standard

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

Cerilliant Quality
ISO 17034
ISO/IEC 17025
ISO 13485
ISO 14001
ISO 9001

Product No.: M-223-1ML
Lot No.: FC01281901
Description of CRM: 4'-Methyl acetyl fentanyl HCl in Methanol (Solution)
Nominal concentration is adjusted for HCl content.
Retest Date: February 2022 See Stability Section
Storage: Store unopened in freezer (-10 °C to -25 °C).
Shipping: Ambient. See Stability Section
Chemical formula: $C_{22}H_{28}N_2O \bullet HCl$
CAS No.: 1071703-95-1
Regulatory: USDEA Schedule I



Analyte	Certified Concentration ± 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

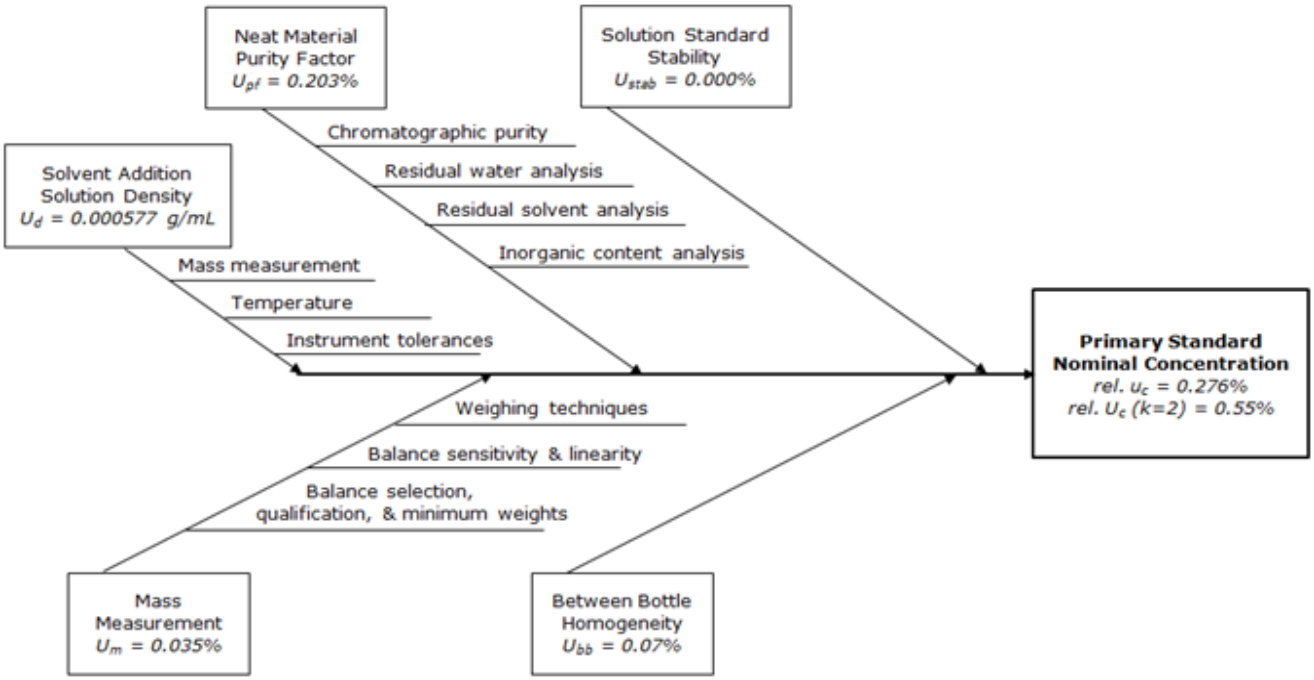
March 05, 2021
Issue Date

Cerilliant 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.



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Details on metrological traceability:

- This standard has been gravimetrically prepared using balances that have been fully qualified and calibrated to ISO 17025 requirements. All calibrations utilize NIST traceable weights which are calibrated externally by a qualified ISO 17025 accredited calibration laboratory to NIST standards. Qualification of each balance includes the assignment of a minimum weighing by a qualified and ISO 17025 accredited calibration vendor taking into consideration the balance and installed environmental conditions to ensure compliance with USP tolerances of NMT 0.10% relative error.
- Fill volume to predetermined specifications is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- The density and material Mass Balance Purity Factor of each raw material is traceable to the SI and higher order reference materials through mass measurement and instrument qualification and calibrations.

Details about certification process:

This standard has been prepared and certified under the ISO 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:	1.2 mL/min		
Wavelength:	210 nm		

		Verified Concentration (mg/mL)	**%RSD - Homogeneity**
Standard Solution	**Lot Number**	**Actual Results**	**Actual Results**
New Lot	FC01281901	0.995	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.

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Analyte Certification - Mass Balance Purity Factor

Each analyte is thoroughly identified and characterized using an orthogonal approach. A mass balance purity factor is assigned incorporating chromatographic purity and residual impurities. The mass balance purity factor 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 HCl	**Molecular Weight (base):**	336.47
Material Lot:	FC01111901	**Molecular Weight (salt):**	372.93
Chemical Formula:	$C_{22}H_{28}N_2O \bullet HCl$	**Salt Adjustment:**	1.108
CAS Number:	1071703-95-1		

Material Characterization Summary

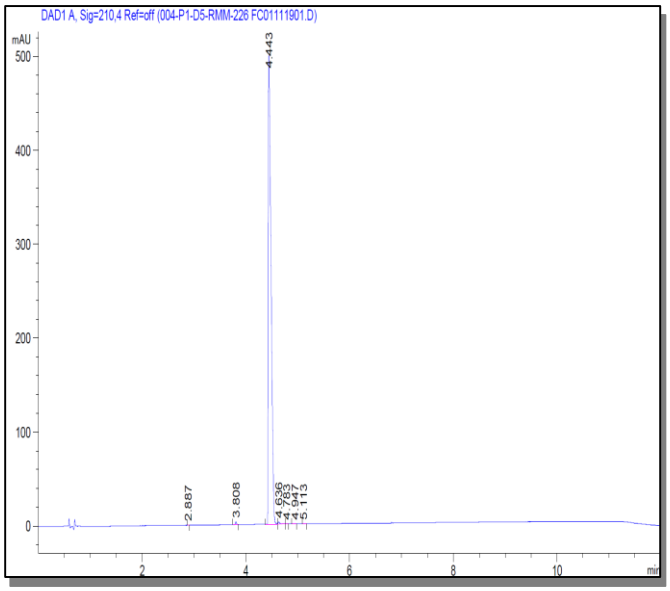
Analytical Test	Method	Results
Primary Chromatographic Purity by HPLC/UV Analysis	SP10-0102	99.5%
Secondary Chromatographic Purity by GC/FID Analysis	SP10-0101	99.6%
Identity by LC/MS Analysis	SP10-0107	Consistent with Structure
Identity by ^{1}H-NMR Analysis	USP <761>, SP10-0116	Consistent with Structure
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 Express C18, 2.7 µm, 3.0 x 100 mm

Mobile Phase: A: Acetonitrile
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/min

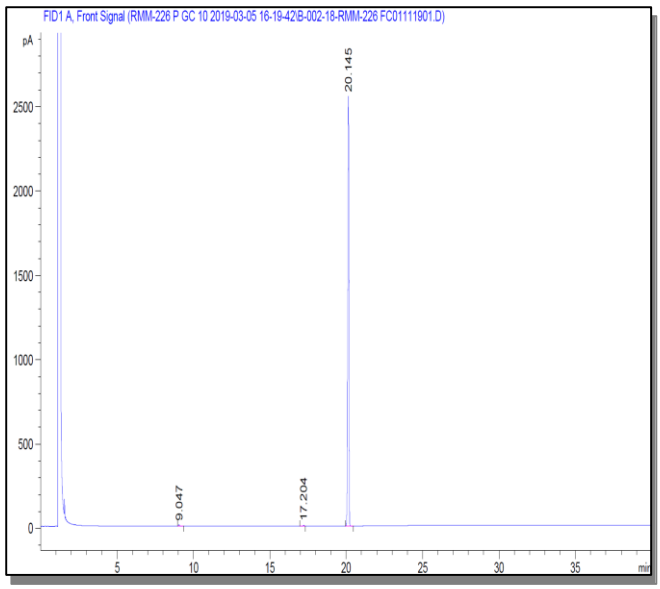
Wavelength: 210 nm

Sample Name: FC01111901

Acquired: 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
7	5.11	0.02

GC/FID



Column: DB-5ms, 30 m x 0.53 mm ID, 1.5 µm film thickness

Temp Program: 40°C to 200°C at 40°C/min
200°C to 300°C at 5°C/min
hold 16 min

Injector Temp: Cool-on-Column

Detector Temp: 325°C

Sample Name: FC01111901

Acquired: March 05, 2019

Peak #	Ret Time	Area %
1	9.05	0.23
2	17.20	0.18
3	20.15	99.59

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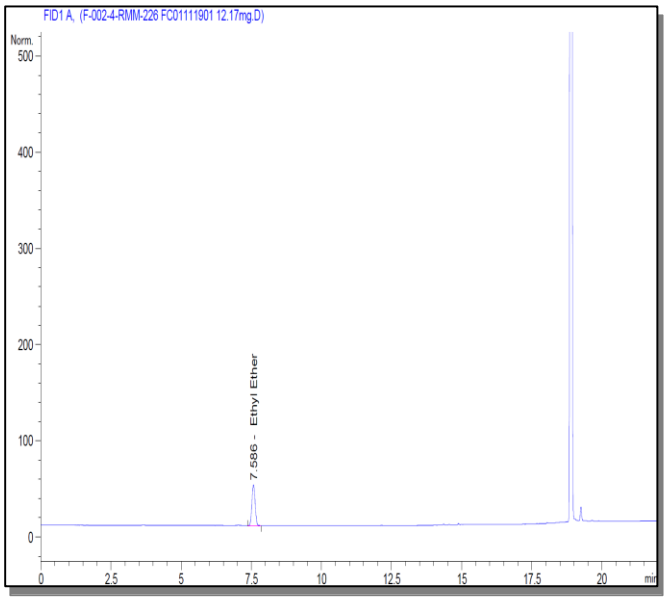
Spectral and Physical Data (cont.)

Residual Solvent Analysis by GC/FID Headspace

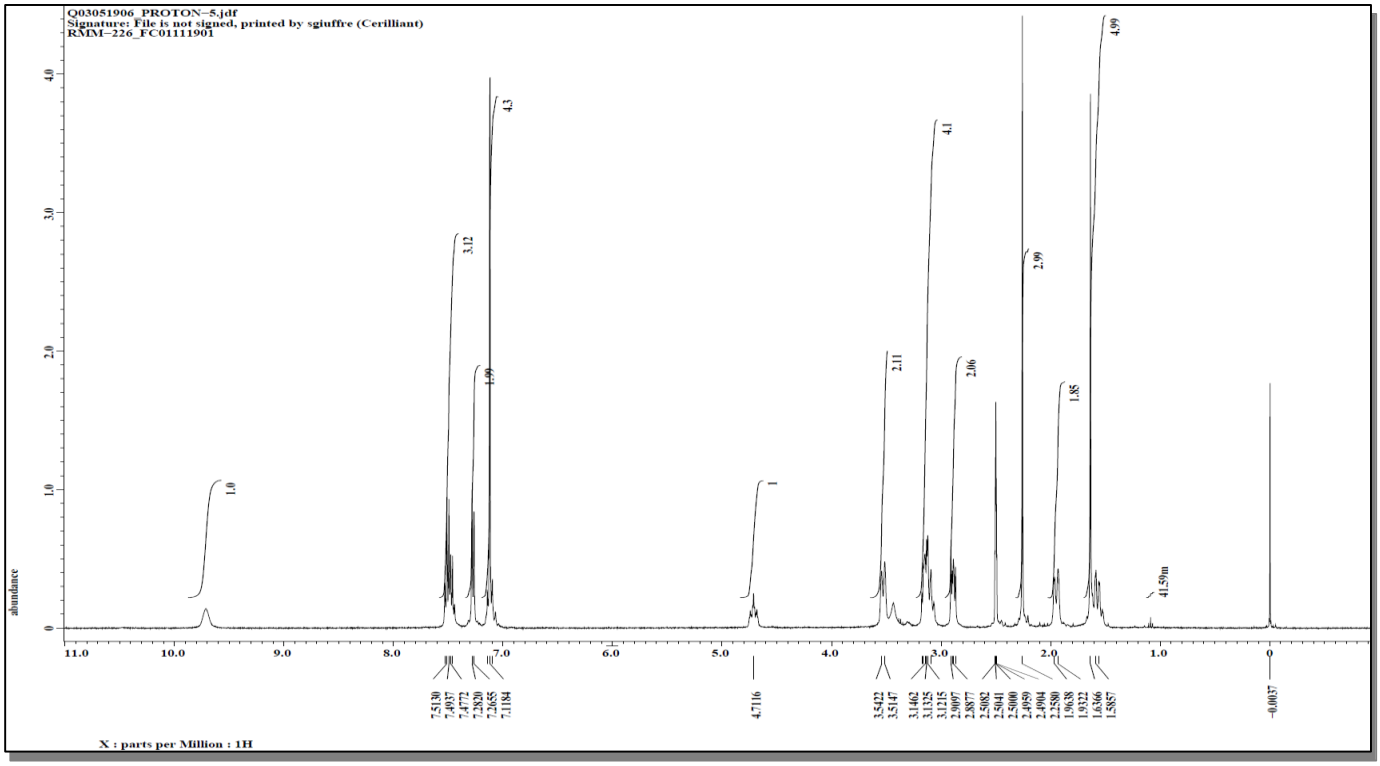


Column:	DB-ALC1 30 m x 0.53 mm, 3 µm film thickness
Temp Program:	40°C hold 12 min to 220°C at 40°C/min hold 5.5 min
Carrier Gas:	Helium
Flow Rate:	2.0 mL/min
Detector Heater Temp:	250°C
Injector:	Headspace Sampler
HS Oven Temp:	60°C
Vial Equilibration:	10 minutes
Sample Name:	FC01111901
Acquired:	March 08, 2019

Peak	Compound	Area	Weight %
1	Ethyl ether	338.55	0.12
2	NMP	NA	NA
Total			**0.12**

^{1}H NMR

Instrument: JEOL ECS 400
Solvent: DMSO-D_6



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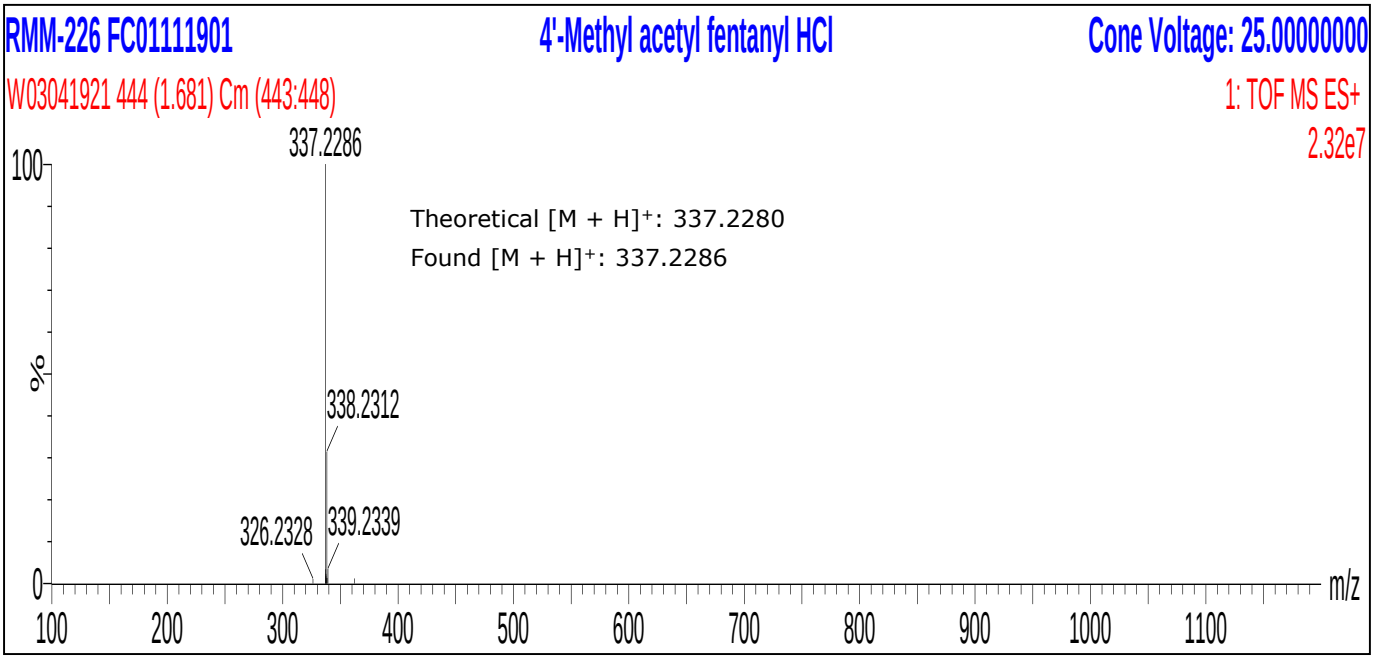
Spectral and Physical Data (cont.)

LC/MS

Column:	Ascentis Express C18, 2.7 µm, 3.0 x 50 mm	**Flow Rate:**	0.4 mL/min
Mobile Phase:	A: 0.1% Formic acid in Water B: Acetonitrile	**Scan Range:**	100-1200 amu
		Ionization:	Electrospray, Positive Ion
		Instrument:	Waters XEVO G2 QTOF
Gradient:		**Acquired:**	March 04, 2019

Time (min)	% A	% B
0.0	80	20
0.5	80	20
4.0	20	80
5.8	20	80
6.0	80	20
8.0	80	20



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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 this product is listed below.*

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

Transport/Shipping: *Stability studies support the transport of this product at ambient conditions.*

Long Term Stability: *Long term stability has been assessed for Freezer storage (-10 °C to -25 °C) conditions. Stability of a minimum of 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.
		Added Long Term Stability Section.
03	March 05, 2021	Revised Retest Date April 2021 to February 2022.

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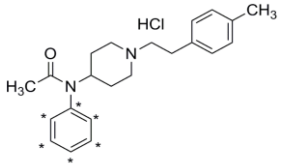
Certified Reference Material - Certificate of Analysis

4'-Methyl acetyl fentanyl-$^{13}C_6$, Primary Measurement Standard

N-[1-[2-(4-methylphenyl)ethyl]-4-piperidinyl]-N-phenyl-acetamide-$^{13}C_6$ HCl

Cerilliant Quality
ISO 17034
ISO/IEC 17025
ISO 13485
ISO 14001
ISO 9001

Product No.: M-224-1ML
Lot No.: FC01241902
Description of CRM: 4'-Methyl acetyl fentanyl-$^{13}C_6$ HCl in Methanol (Solution)
Nominal concentration is adjusted for HCl content.
Retest Date: February 2022 See Stability Section
Storage: Store unopened in freezer (-10 °C to -25 °C).
Shipping: Ambient. See Stability Section
Chemical formula: $C_{16}{}^{13}C_6H_{28}N_2O \bullet HCl$
CAS No.: NA
Regulatory: USDEA Schedule I



Analyte	Certified Concentration ± 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.

Darron Ellsworth, Quality Assurance Manager

March 05, 2021
Issue Date

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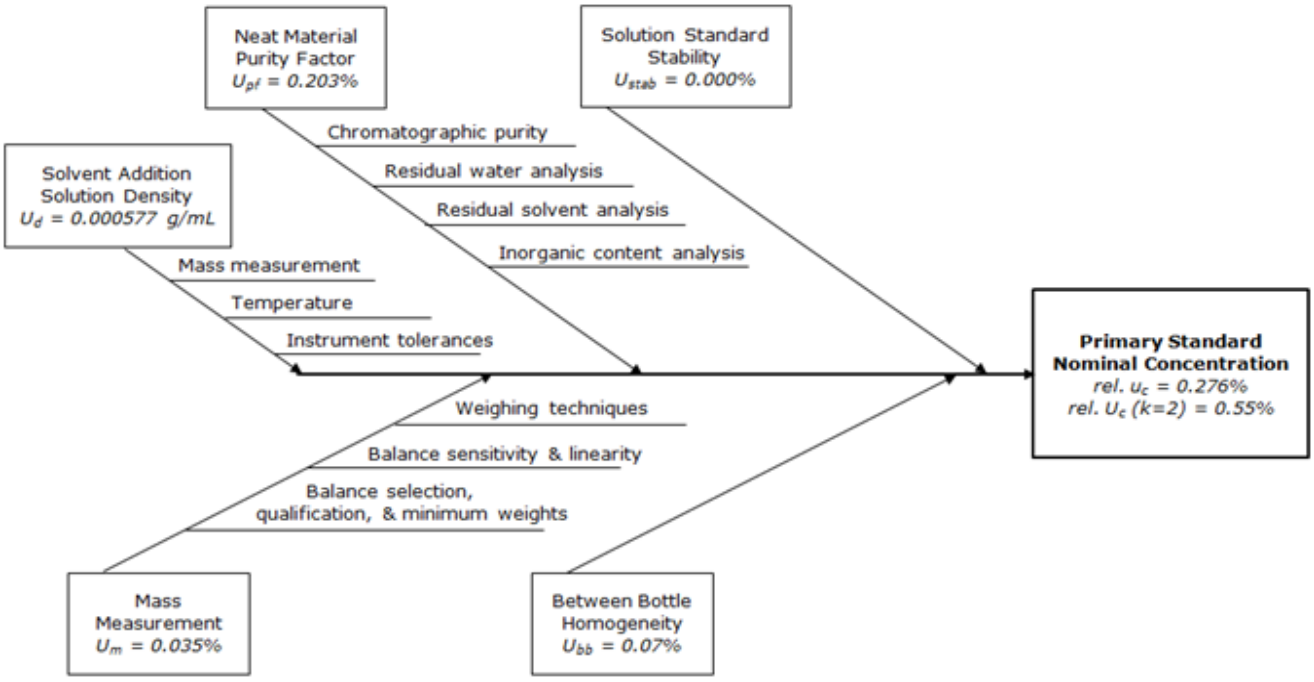
Packaging:	2 mL amber USP Type 1 glass ampoule containing not less than 1 mL of certified solution. Ampoules are overfilled to ensure a minimum of 1 mL volume can be transferred when using a 1mL Class A volumetric pipette.
Details on starting materials:	Each raw material utilized has been identified 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.



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Details on metrological traceability:

- This standard has been gravimetrically prepared using balances that have been fully qualified and calibrated to ISO 17025 requirements. All calibrations utilize NIST traceable weights which are calibrated externally by a qualified ISO 17025 accredited calibration laboratory to NIST standards. Qualification of each balance includes the assignment of a minimum weighing by a qualified and ISO 17025 accredited calibration vendor taking into consideration the balance and installed environmental conditions to ensure compliance with USP tolerances of NMT 0.10% relative error.
- Fill volume to predetermined specifications is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- The density and material Mass Balance Purity Factor of each raw material is traceable to the SI and higher order reference materials through mass measurement and instrument qualification and calibrations.

Details about certification process:

This standard has been prepared and certified under the ISO 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:	1.3 mL/min		
Wavelength:	210 nm		

		Verified Concentration (mg/mL)	**%RSD - Homogeneity**
Standard Solution	**Lot Number**	**Actual Results**	**Actual Results**
New Lot	FC01241902	1.006	1.8

- 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:	4'-Methyl acetyl fentanyl-$^{13}C_6$ HCl	**Molecular Weight (base):**	342.43
Material Lot:	FC01111903	**Molecular Weight (salt):**	378.89
Chemical Formula:	$C_{16}{}^{13}C_6H_{28}N_2O\bullet HCl$	**Salt Adjustment:**	1.106
CAS Number:	NA		

Material Characterization Summary

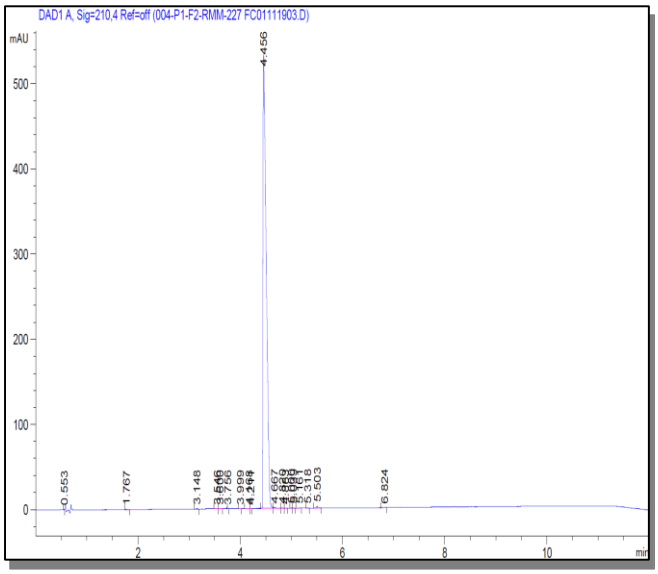
Analytical Test	**Method**	**Results**	
Primary Chromatographic Purity by HPLC/UV Analysis	SP10-0102	99.5%	
Secondary Chromatographic Purity by GC/FID Analysis	SP10-0101	99.7%	
Identity by LC/MS Analysis	SP10-0107	Consistent with Structure	
Isotopic Purity and Distribution by LC/MS SIM Analysis	SP10-0107	0.00% $^{13}C_0$ vs $^{13}C_6$	
		0.00% $^{13}C_0$	0.08% $^{13}C_4$
		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 Analysis	USP <761>, SP10-0116	Consistent with Structure	
Residual Solvent Analysis by GC/FID Headspace	AM1087 [1]	None Detected	
Residual Water Analysis by Karl Fischer Coulometry	AM1346 [1]	Below Quantitation Limit	
Inorganic Content by Microash Analysis	SP10-0135	< 0.2%	
Mass Balance Purity Factor		99.48%	

[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: Ascentis Express C18, 2.7 µm, 3.0 x 100 mm

Mobile Phase: A: Acetonitrile
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/min

Wavelength: 210 nm

Sample Name: FC01111903

Acquired: February 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

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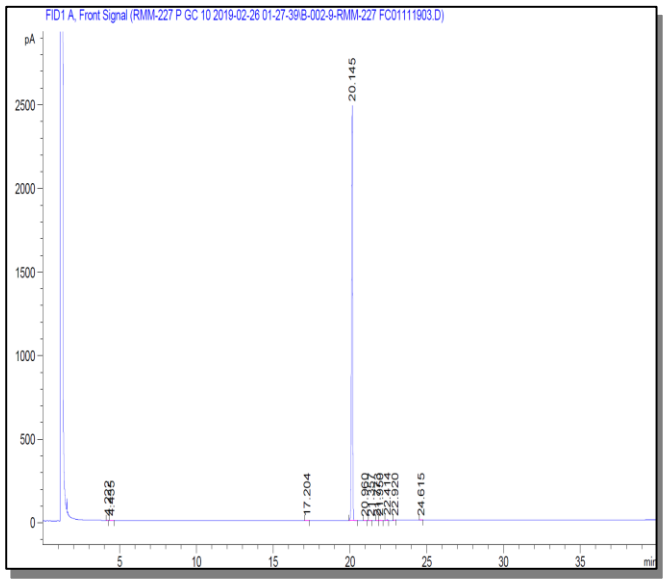
Spectral and Physical Data (cont.)

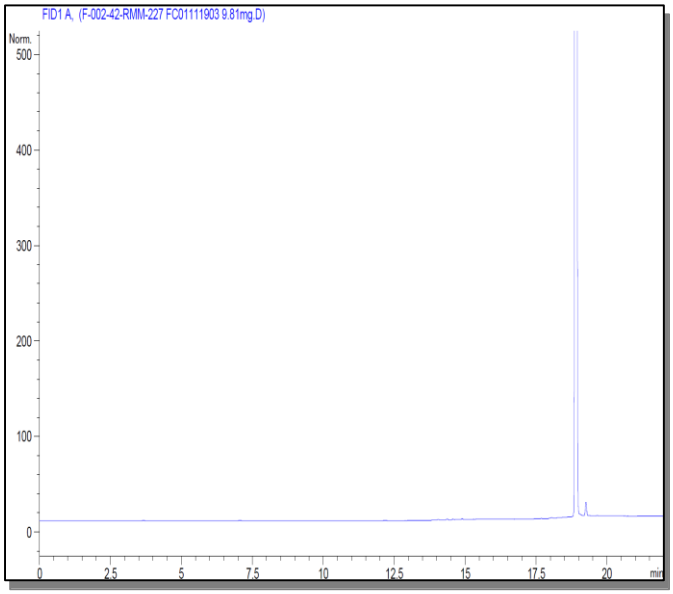
GC/FID



Column:	DB-5ms, 30 m x 0.53 mm ID, 1.5 µm film thickness
Temp Program:	40°C to 200°C at 40°C/min 200°C to 300°C at 5°C/min hold 16 min
Injector Temp:	Cool-on-Column
Detector Temp:	325°C
Sample Name:	FC01111903
Acquired:	February 26, 2019

Peak #	Ret Time	Area %
1	4.22	0.01
2	4.44	0.01
3	17.20	0.06
4	20.15	99.73
5	20.96	0.01
6	21.36	0.02
7	21.77	0.01
8	21.95	0.03
9	22.41	0.12
10	22.92	0.00
11	24.62	0.00

Residual Solvent Analysis by GC/FID Headspace



Column:	DB-ALC1 30 m x 0.53 mm, 3 µm film thickness
Temp Program:	40°C hold 12 min to 220°C at 40°C/min hold 5.5 min
Carrier Gas:	Helium
Flow Rate:	2.0 mL/min
Detector Heater Temp:	250°C
Injector:	Headspace Sampler
HS Oven Temp:	60°C
Vial Equilibration:	10 minutes
Sample Name:	FC01111903
Acquired:	February 26, 2019

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

ND - None Detected

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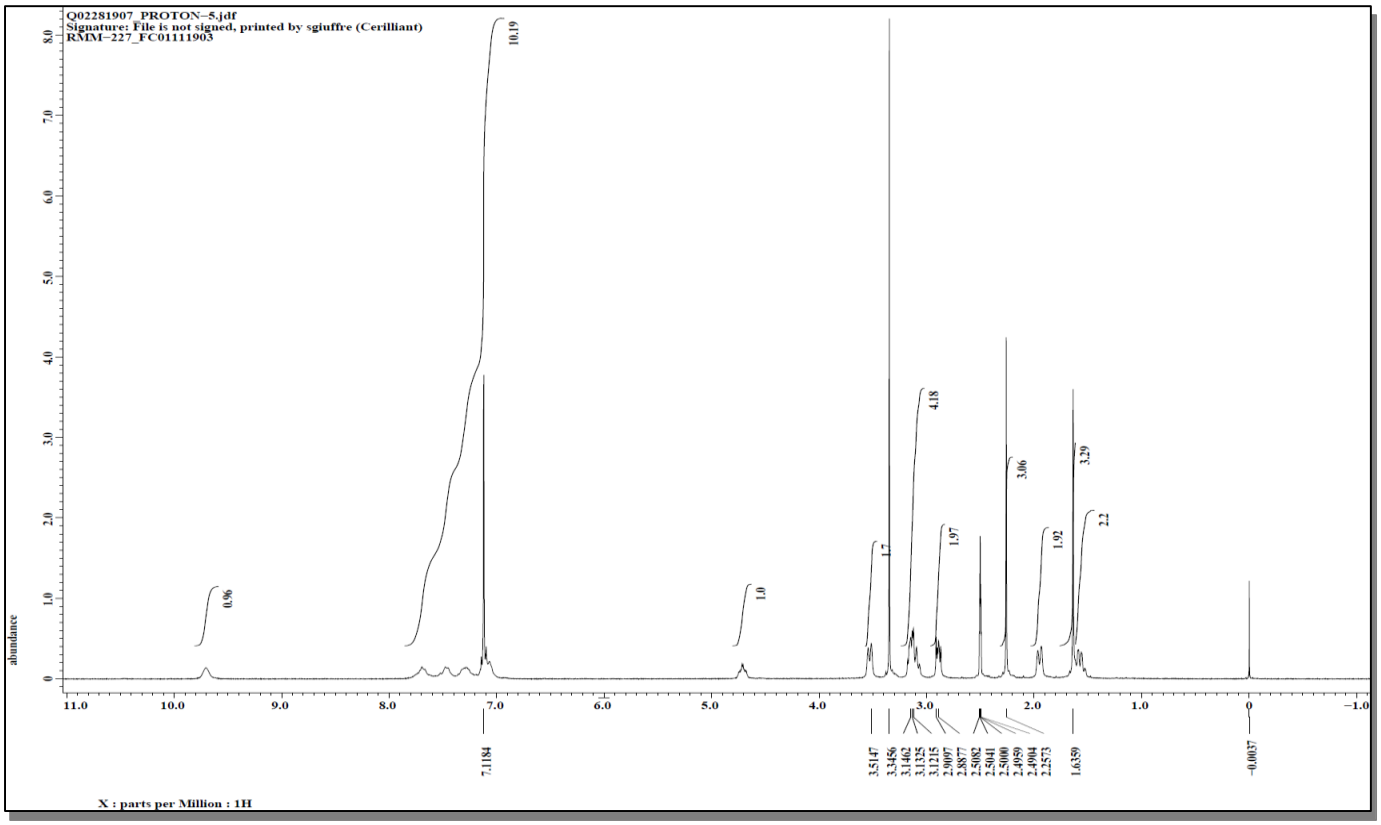
Spectral and Physical Data (cont.)

^{1}H NMR

Instrument: JEOL ECS 400
Solvent: DMSO-D_6



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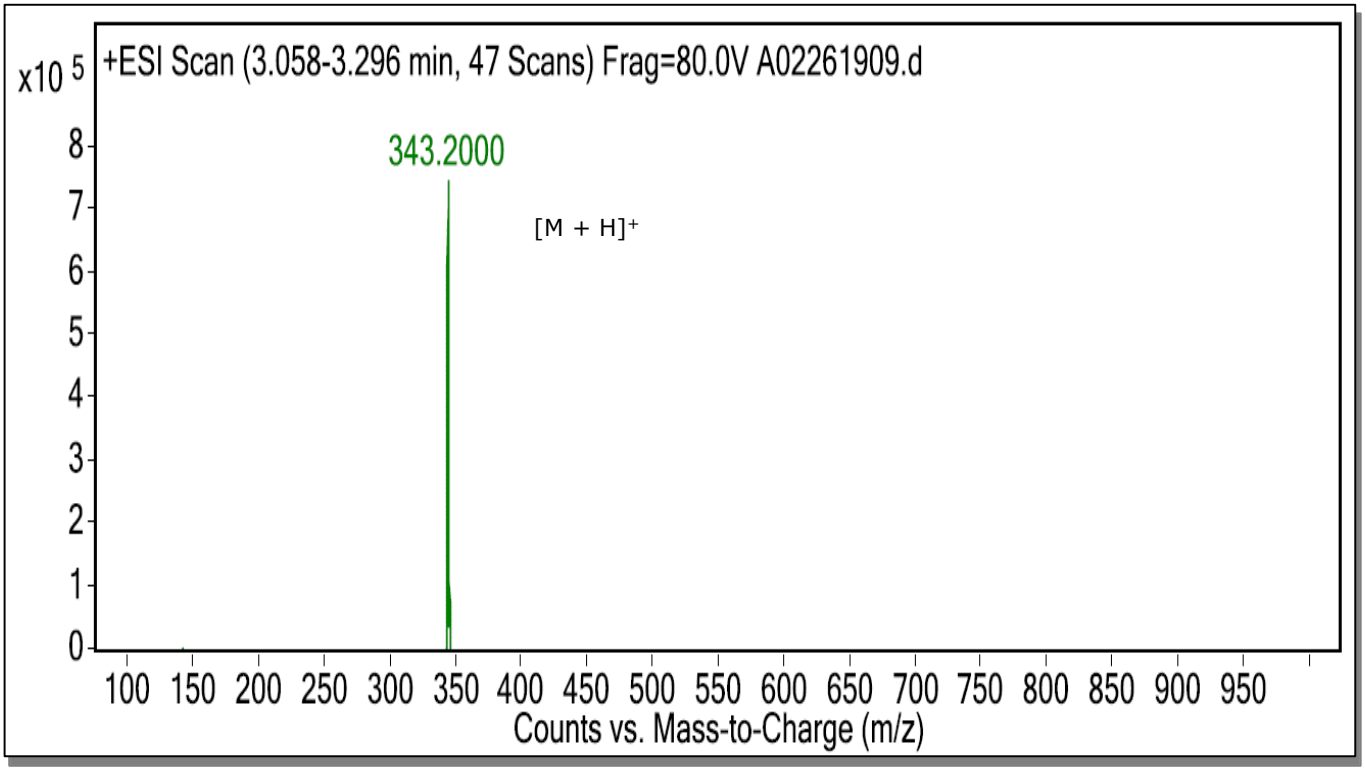
Spectral and Physical Data (cont.)

LC/MS

Column: Kinetex C18, 2.6 µm, 2.1 x 50 mm
Mobile Phase: A: 0.1% Formic acid in Water
B: Acetonitrile
Gradient:

Time (min)	% A	% B
0.0	80	20
5.0	20	80
6.0	20	80
7.0	80	20
11.0	80	20

Flow Rate: 0.5 mL/min
Scan Range: 100-1000 amu
Ionization: Electrospray, Positive Ion
Instrument: Agilent 6410A Mass Spectrometer
Acquired: February 26, 2019



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Spectral and Physical Data (cont.)

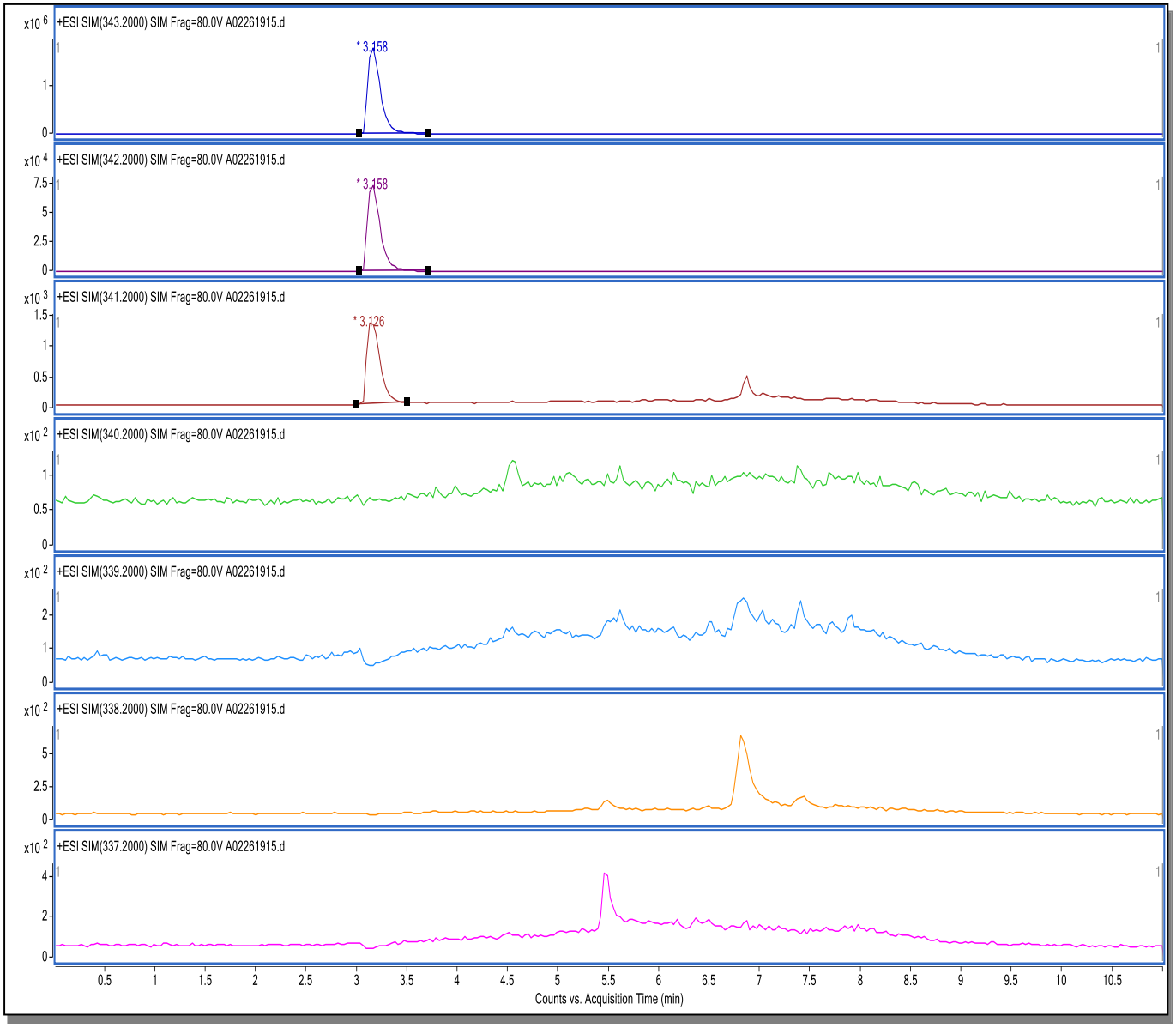
Isotopic Purity by LC/MS SIM

Column: Kinetex C18, 2.6 µm, 2.1 x 50 mm
Mobile Phase: A: 0.1% Formic acid in Water
B: Acetonitrile

Gradient:

Time (min)	% A	% B
0.0	80	20
5.0	20	80
6.0	20	80
7.0	80	20
11.0	80	20

Flow Rate: 0.5 mL/min
Scan Range: 337-343 amu
Ionization: Electrospray, Positive Ion
Instrument: Agilent 6410A Mass Spectrometer
Acquired: February 26, 2019



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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 (M-223-1ML, 4'-Methyl acetyl fentanyl HCl) is listed below.*

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

Transport/Shipping: *Stability studies support the transport of this product at ambient conditions.*

Long Term Stability: *Long term stability has been assessed for Freezer storage (-10 °C to -25 °C) conditions. Stability of a minimum of 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

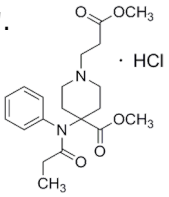
Revision No.	Date	Reason for Revision
00	March 29, 2019	Initial version.
01	May 10, 2019	Updated Short Term Stability to include four week stability data.
02	May 04, 2020	Revised Retest Date May 2020 to April 2021.
		Added Long Term Stability Section.
03	March 05, 2021	Revised Retest Date of April 2021 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
Lot No.: FC01141905
Description of CRM: Remifentanil HCl in Methanol (Solution)
Nominal concentration is adjusted for HCl content.
Retest Date: February 2022 See Section "Stability Assessment".
Storage: Store unopened in freezer (-10 °C to -25 °C).
Shipping: Ship cold. See Section "Stability Assessment".
Chemical formula: $C_{20}H_{28}N_2O_5 \bullet HCl$
CAS No.: 132539-07-2
Regulatory: USDEA Schedule II



Cerilliant Quality
ISO 17034
ISO/IEC 17025
ISO 13485
ISO 14001
ISO 9001

Analyte	Certified Concentration ± associated uncertainty U, u=k*u (k=2)
Remifentanil	**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 02, 2021
Issue Date

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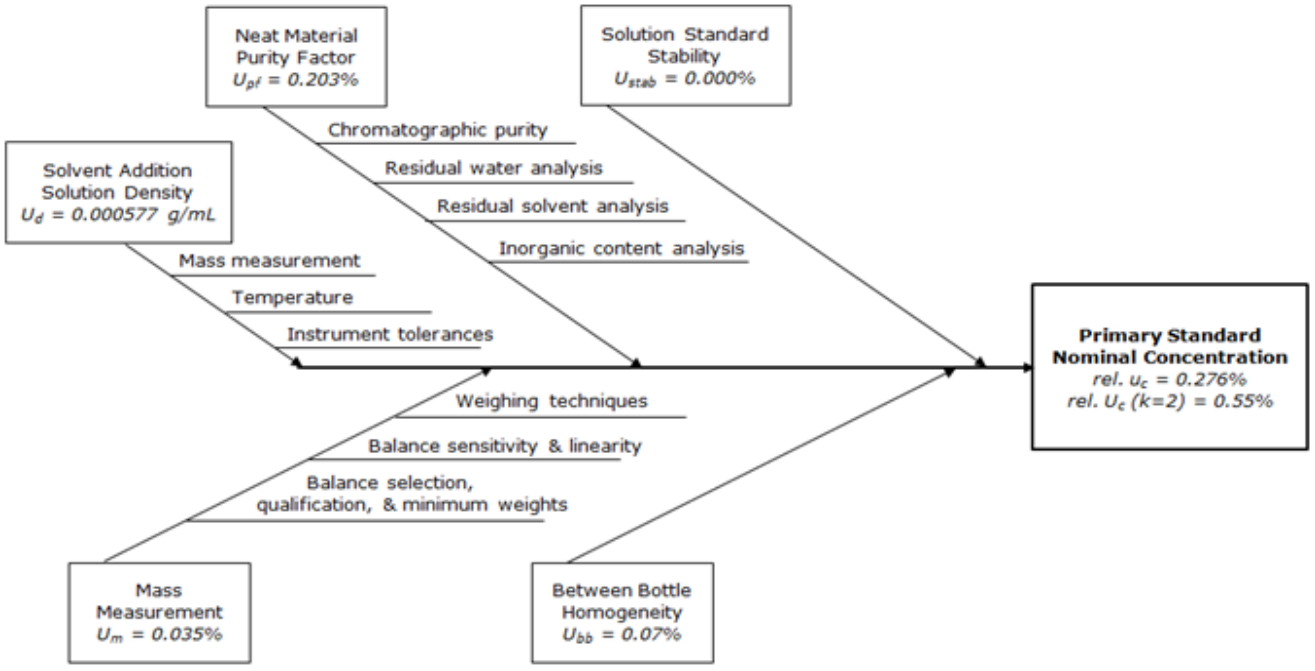
Packaging:	2 mL amber USP Type 1 glass ampoule containing not less than 1 mL of certified solution. Ampoules are overfilled to ensure a minimum of 1 mL volume can be transferred when using a 1mL Class A volumetric pipette.
Details on starting materials:	Each raw material utilized has been identified 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.



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Details on metrological traceability:

- This standard has been gravimetrically prepared using balances that have been fully qualified and calibrated to ISO 17025 requirements. All calibrations utilize NIST traceable weights which are calibrated externally by a qualified ISO 17025 accredited calibration laboratory to NIST standards. Qualification of each balance includes the assignment of a minimum weighing by a qualified and ISO 17025 accredited calibration vendor taking into consideration the balance and installed environmental conditions to ensure compliance with USP tolerances of NMT 0.10% relative error.
- Fill volume to predetermined specifications is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- The density and material Mass Balance Purity Factor of each raw material is traceable to the SI and higher order reference materials through mass measurement and instrument qualification and calibrations.

Details about certification process:

This standard has been prepared and certified under the ISO 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.

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

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:	1.5 mL/min		
Wavelength:	210 nm		

		Verified Concentration (mg/mL)	**%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.

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Analyte Certification - Mass Balance Purity Factor

Each analyte is thoroughly identified and characterized using an orthogonal approach. A mass balance purity factor is assigned incorporating chromatographic purity and residual impurities. The mass balance purity factor and salt adjustment are utilized to calculate the weighing adjustment necessary to ensure accuracy of the solution standard concentration.

Material Name:	Remifentanil HCl	**Molecular Weight (base):**	376.45
Material Lot:	FC09271801	**Molecular Weight (salt):**	412.91
Chemical Formula:	$C_{20}H_{28}N_2O_5$ • HCl	**Salt Adjustment:**	1.097
CAS Number:	132539-07-2		

Material Characterization 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 Factor		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.

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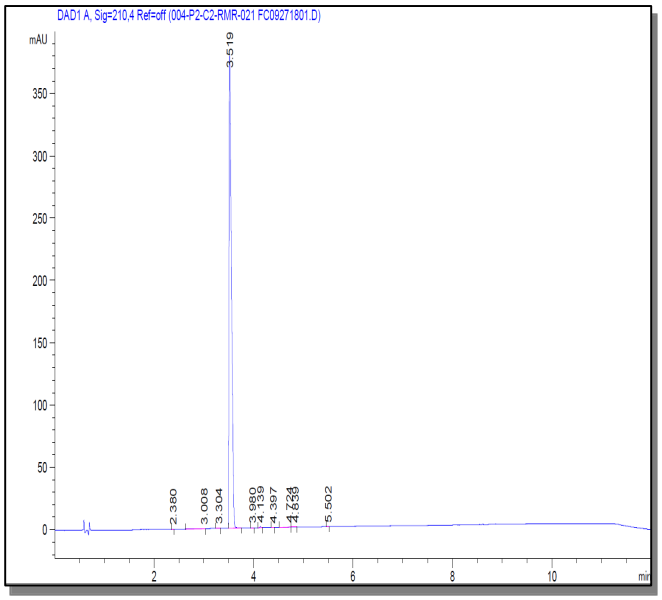
Spectral and Physical Data

HPLC/UV



Column: Ascentis Express C18, 2.7 µm, 3.0 x 100 mm

Mobile Phase: A: Acetonitrile
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/min

Wavelength: 210 nm

Sample Name: FC09271801

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
9	4.84	0.01
10	5.50	0.01

Peak #3 has been identified as Remifentanil acid

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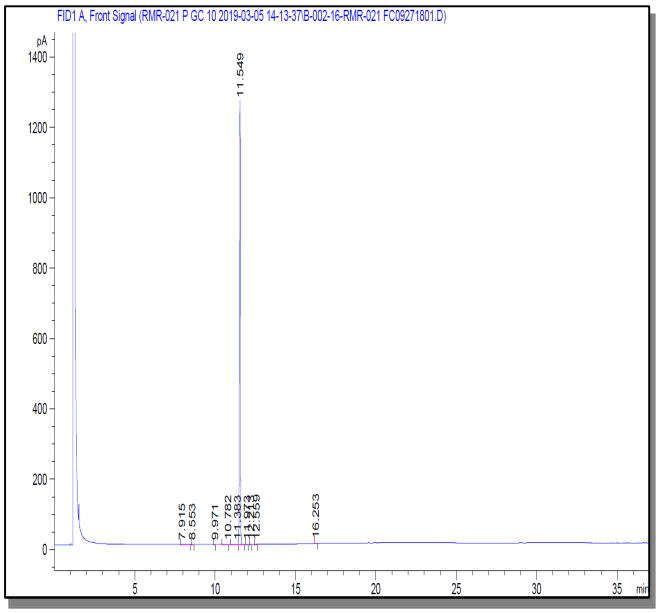
Spectral and Physical Data (cont.)

GC/FID

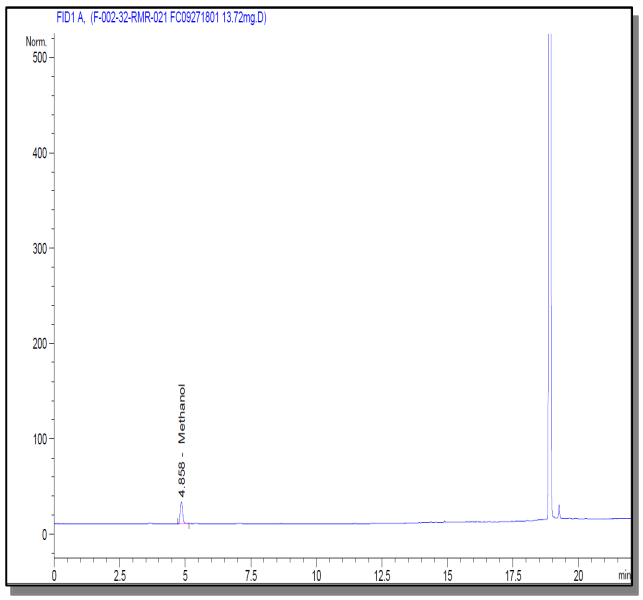


Column: DB-5ms, 30 m x 0.53 mm ID, 1.5 µm film thickness
Temp Program: 40°C to 240°C at 40°C/min
240°C to 300°C at 5°C/min
hold 20 min
Injector Temp: Cool-on-Column
Detector Temp: 325°C

Sample Name: FC09271801
Acquired: March 05, 2019

Peak #	Ret Time	Area %
1	7.92	0.10
2	8.55	0.00
3	9.97	0.00
4	10.78	0.02
5	11.38	0.03
6	11.55	99.73
7	11.97	0.01
8	12.21	0.01
9	12.56	0.01
10	16.25	0.09

Residual Solvent Analysis by GC/FID Headspace



Column: DB-ALC1 30 m x 0.53 mm, 3 µm film thickness
Temp Program: 40°C hold 12 min to 220°C at 40°C/min hold 5.5 min
Carrier Gas: Helium
Flow Rate: 2.0 mL/min
Detector Heater Temp: 250°C
Injector: Headspace Sampler
HS Oven Temp: 60°C
Vial Equilibration: 10 minutes

Sample Name: FC09271801
Acquired: February 28, 2019

Peak	Compound	Area	Weight %
1	Methanol	147.35	0.93
2	NMP	NA	NA
Total			**0.93**

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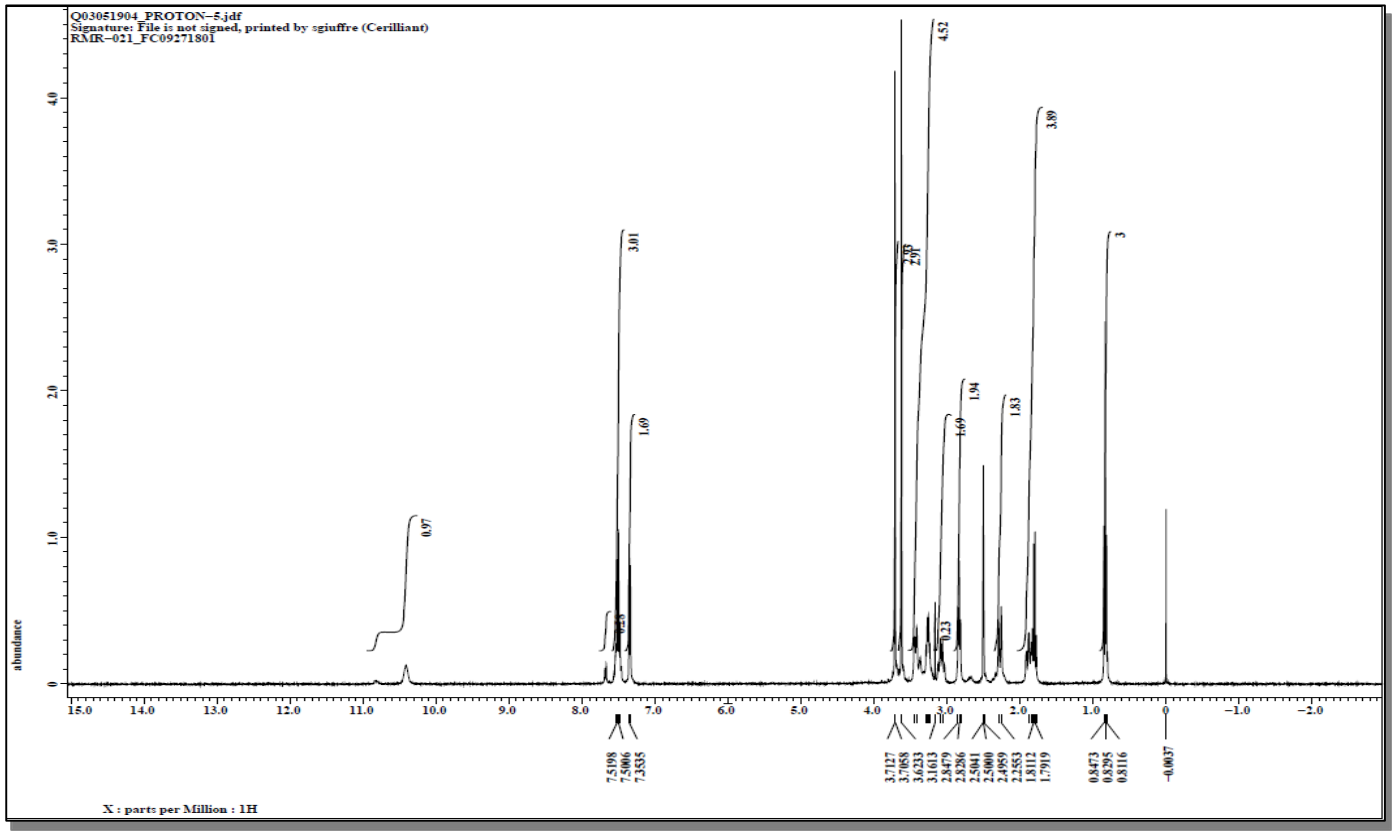
Spectral and Physical Data (cont.)

^{1}H NMR

Instrument: JEOL ECS 400
Solvent: DMSO-D_6



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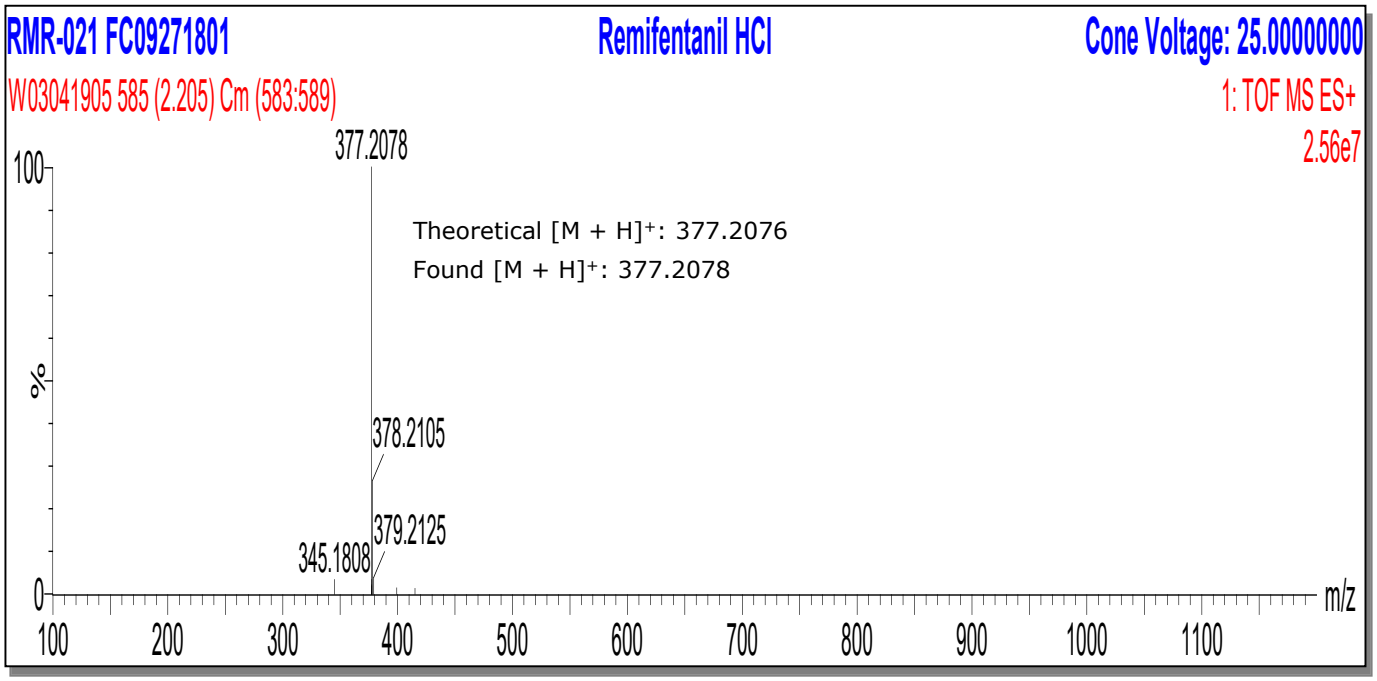
Spectral and Physical Data (cont.)

LC/MS

Column:	Ascentis Express C18, 2.7 µm, 3.0 x 50 mm	**Flow Rate:**	0.4 mL/min
Mobile Phase:	A: 0.1% Formic acid in Water B: Acetonitrile	**Scan Range:**	100-1200 amu
		Ionization:	Electrospray, Positive Ion
		Instrument:	Waters XEVO G2 QTOF
Gradient:		**Acquired:**	March 04, 2019

Time (min)	% A	% B
0.0	90	10
0.5	90	10
4.0	50	50
5.8	50	50
6.0	90	10
8.0	90	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 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, 2021	Updated Retest Date of March 2021 to February 2022.
		Update page reference on first page.

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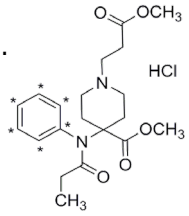
Certified Reference Material - Certificate of Analysis

Remifentanil-$^{13}C_6$, Primary Measurement Standard

3-[Methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-1-piperidine]propanoic acid methyl ester-$^{13}C_6$ HCl

Product No.: R-033-1ML
Lot No.: FC01141906
Description of CRM: Remifentanil-$^{13}C_6$ HCl in Methanol (Solution)
Nominal concentration is adjusted for HCl content.
Retest Date: February 2022 See Section "Stability Assessment".
Storage: Store unopened in freezer (-10 °C to -25 °C).
Shipping: Ship cold. See Section "Stability Assessment".
Chemical formula: $C_{14}{}^{13}C_6H_{28}N_2O_5 \bullet HCl$
CAS No.: NA
Regulatory: USDEA Schedule II

Cerilliant Quality
ISO 17034
ISO/IEC 17025
ISO 13485
ISO 14001
ISO 9001



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 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.

Darron Ellsworth, Quality Assurance Manager

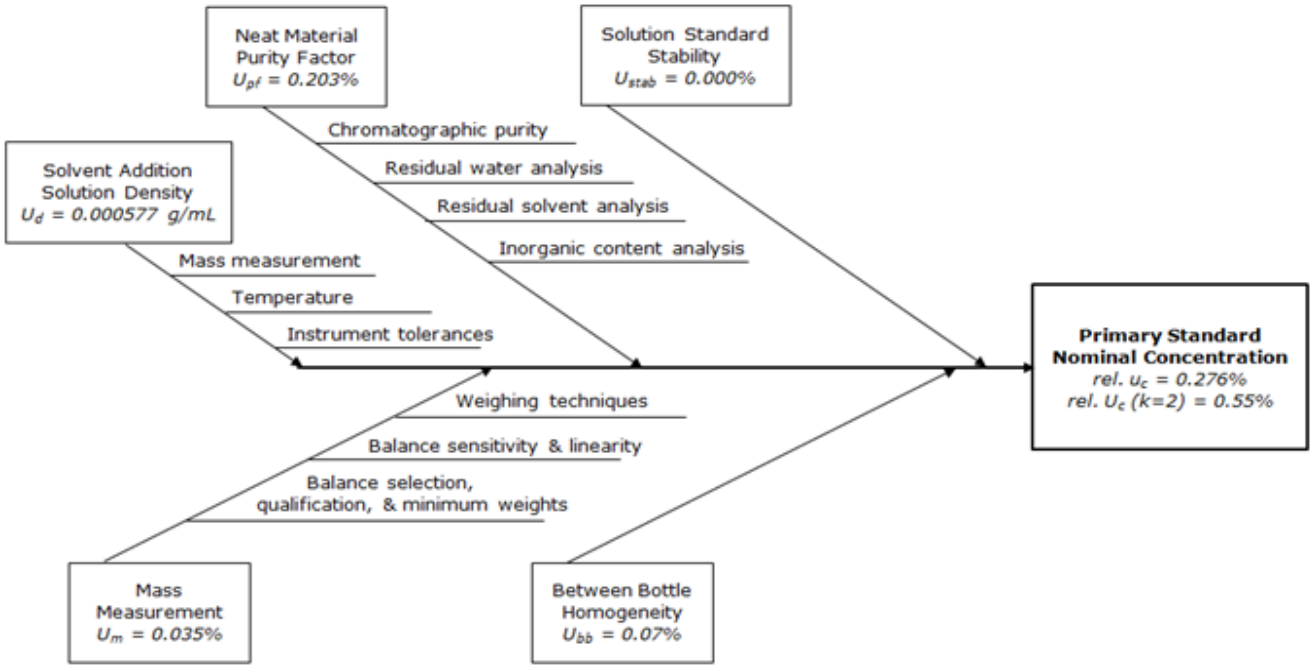
March 02, 2021
Issue Date

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.



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Details on metrological traceability:

- This standard has been gravimetrically prepared using balances that have been fully qualified and calibrated to ISO 17025 requirements. All calibrations utilize NIST traceable weights which are calibrated externally by a qualified ISO 17025 accredited calibration laboratory to NIST standards. Qualification of each balance includes the assignment of a minimum weighing by a qualified and ISO 17025 accredited calibration vendor taking into consideration the balance and installed environmental conditions to ensure compliance with USP tolerances of NMT 0.10% relative error.
- Fill volume to predetermined specifications is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- The density and material Mass Balance Purity Factor of each raw material is traceable to the SI and higher order reference materials through mass measurement and instrument qualification and calibrations.

Details about certification process:

This standard has been prepared and certified under the ISO 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.

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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:	1.5 mL/min		
Wavelength:	210 nm		

		Verified Concentration (mg/mL)	**%RSD - Homogeneity**
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.

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

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:	$C_{14}{}^{13}C_6H_{28}N_2O_5 \bullet HCl$	**Salt Adjustment:**	1.095
CAS Number:	NA		

Material Characterization Summary

Analytical Test	**Method**	**Results**	
Primary Chromatographic Purity by HPLC/UV Analysis	SP10-0102	99.5%	
Secondary Chromatographic Purity by LC/MS Analysis	SP10-0107	> 99.9%	
Identity by LC/MS Analysis	SP10-0107	Consistent with Structure	
Isotopic Purity and Distribution by LC/MS SIM Analysis	SP10-0107	0.01% $^{13}C_0$ vs $^{13}C_6$	
		0.01% $^{13}C_0$	0.09% $^{13}C_4$
		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.

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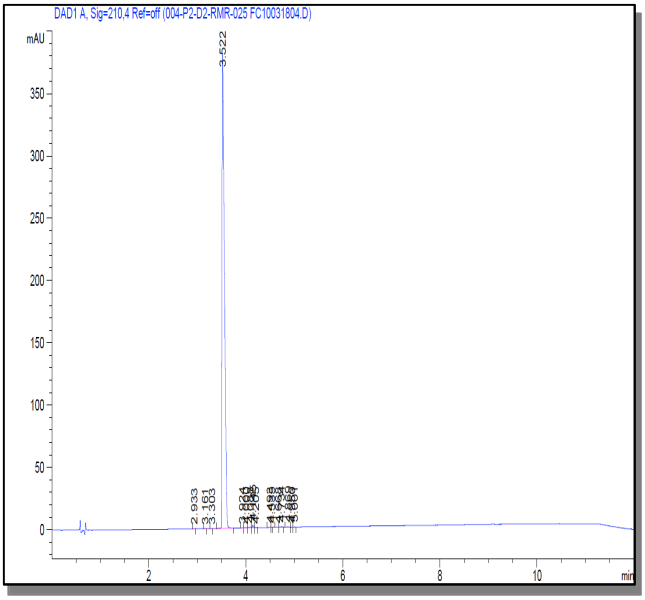
Spectral and Physical Data

HPLC/UV



Column: Ascentis Express C18, 2.7 µm, 3.0 x 100 mm

Mobile Phase: A: Acetonitrile
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/min

Wavelength: 210 nm

Sample Name: FC10031804

Acquired: March 01, 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
15	4.95	0.01
16	5.00	0.01

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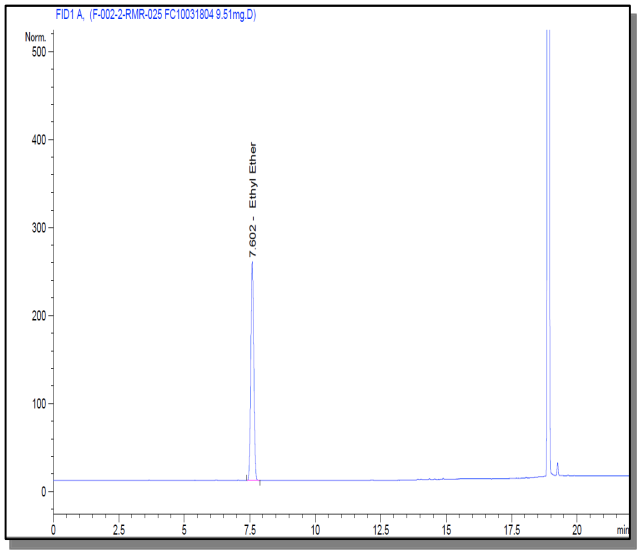
Spectral and Physical Data (cont.)

Residual Solvent Analysis by GC/FID Headspace

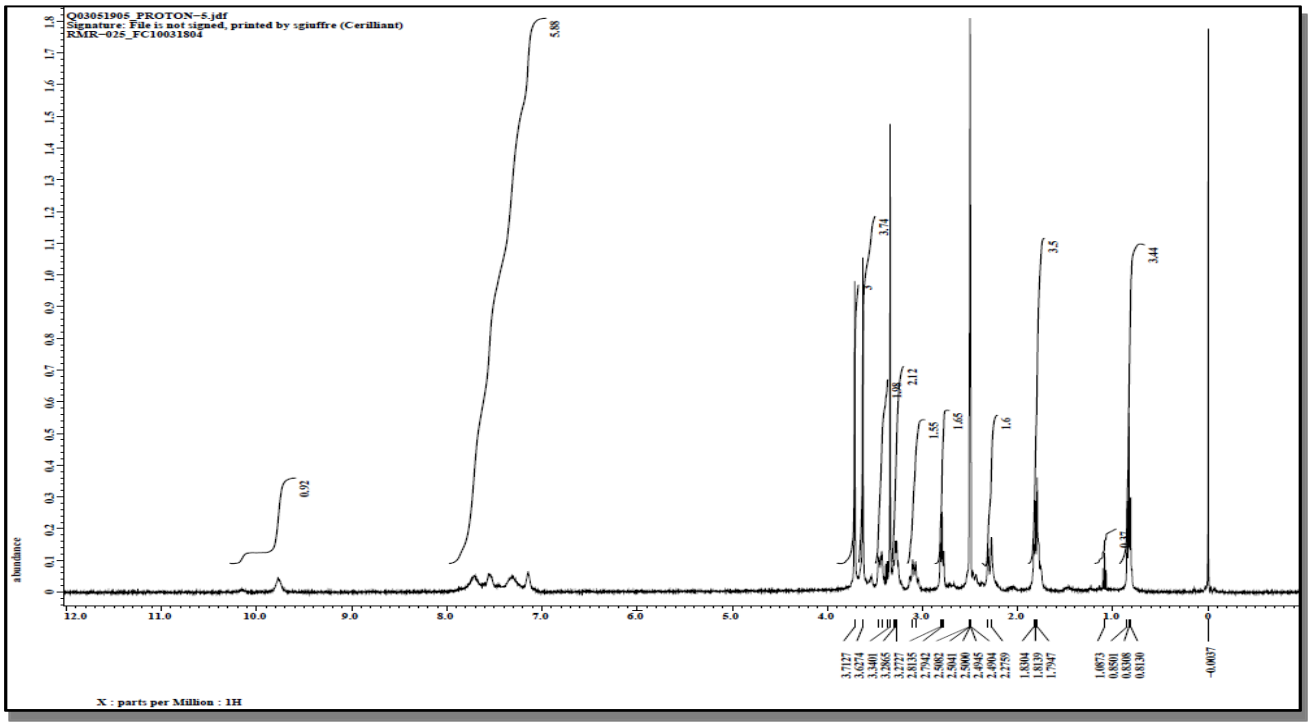


Column:	DB-ALC1 30 m x 0.53 mm, 3 µm film thickness
Temp Program:	40°C hold 12 min to 220°C at 40°C/min hold 5.5 min
Carrier Gas:	Helium
Flow Rate:	2.0 mL/min
Detector Heater Temp:	250°C
Injector:	Headspace Sampler
HS Oven Temp:	60°C
Vial Equilibration:	10 minutes
Sample Name:	FC10031804
Acquired:	March 08, 2019

Peak	Compound	Area	Weight %
1	Ethyl ether	1987.61	0.93
2	NMP	NA	NA
Total			**0.93**

^{1}H NMR

Instrument: JEOL ECS 400
Solvent: DMSO-D_6



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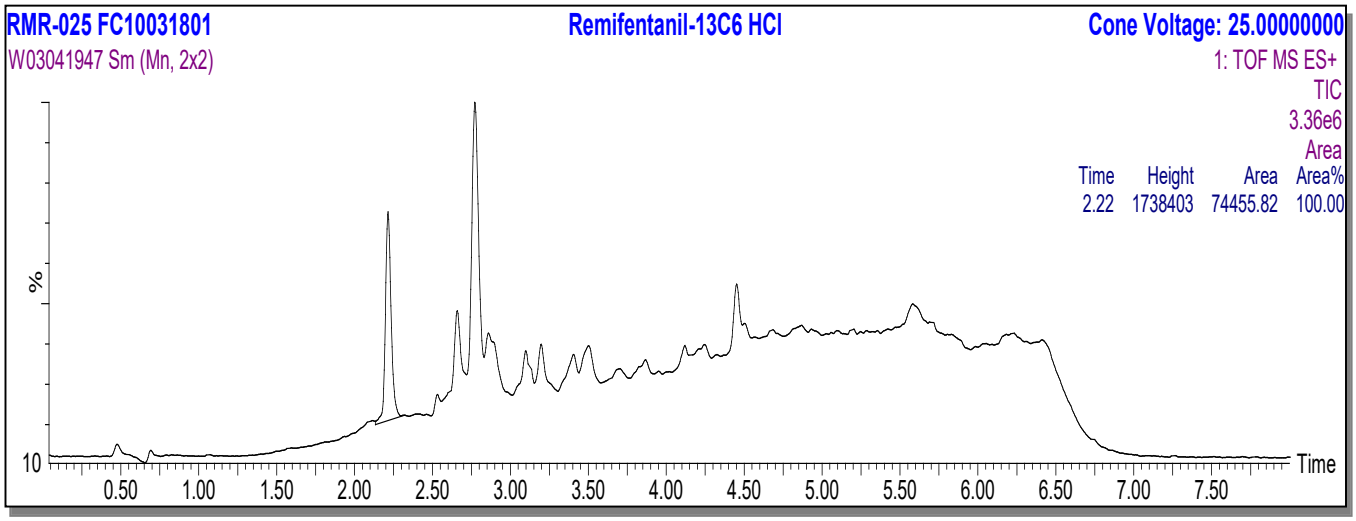
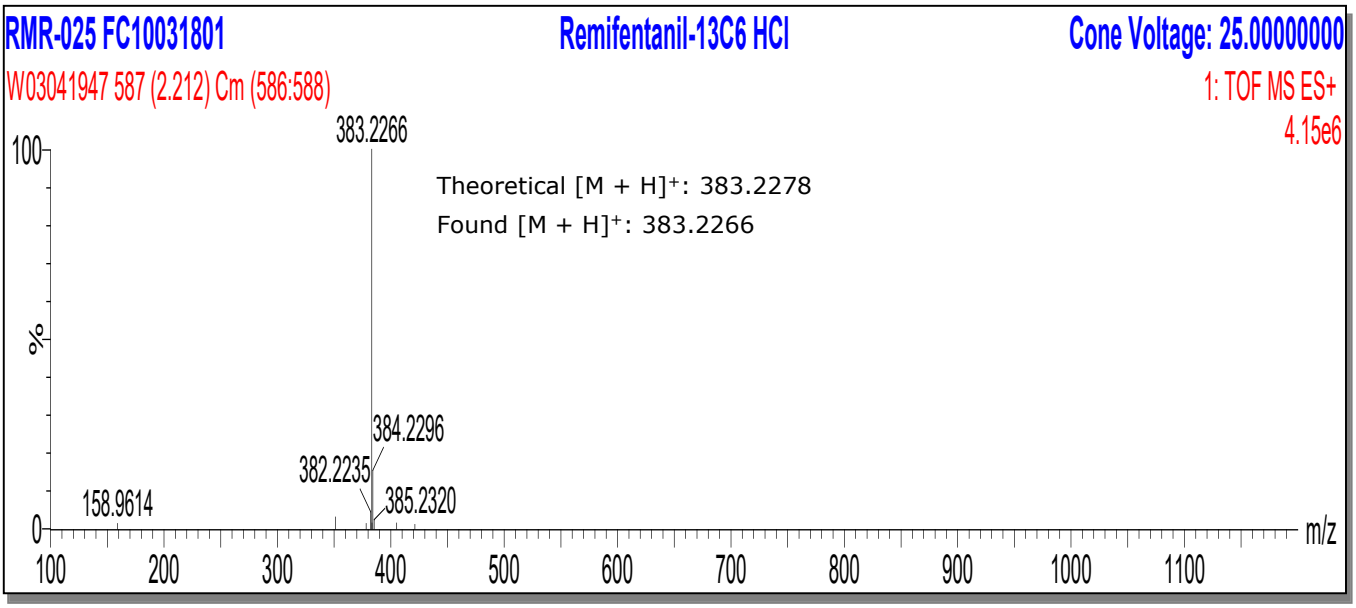
Spectral and Physical Data (cont.)

LC/MS

Column:	Ascentis Express C18, 2.7 µm, 3.0 x 50 mm	**Flow Rate:**	0.4 mL/min
Mobile Phase:	A: 0.1% Formic acid in Water B: Acetonitrile	**Scan Range:**	100-1200 amu
		Ionization:	Electrospray, Positive Ion
		Instrument:	Waters XEVO G2 QTOF
Gradient:		**Acquired:**	March 04, 2019

Time (min)	% A	% B
0.0	90	10
0.5	90	10
4.0	50	50
5.8	50	50
6.0	90	10
8.0	90	10





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Spectral and Physical Data (cont.)

Isotopic Purity by LC/MS SIM

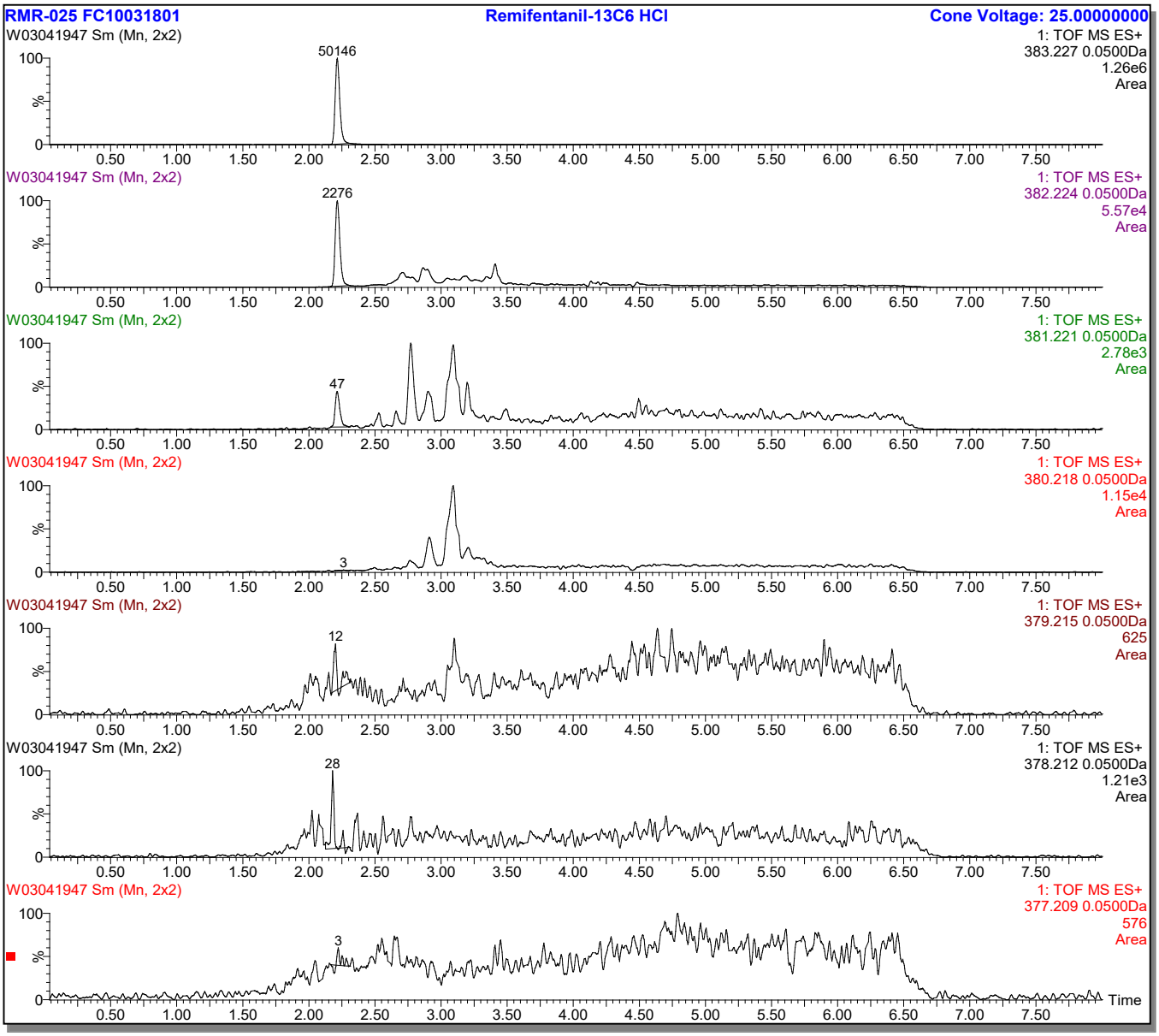
Column: Ascentis Express C18, 2.7 µm, 3.0 x 50 mm

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

Gradient:

Time (min)	% A	% B
0.0	90	10
0.5	90	10
4.0	50	50
5.8	50	50
6.0	90	10
8.0	90	10

Flow Rate: 0.4 mL/min
Scan Range: 377-383 amu
Ionization: Electrospray, Positive Ion
Instrument: Waters XEVO G2 QTOF
Acquired: March 04, 2019



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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 (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 after four weeks.
Refrigerator	4°C	
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.

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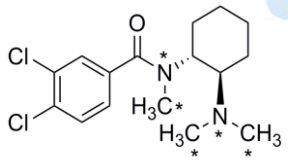
Certified Reference Material - Certificate of Analysis

U-47700-$^{13}C_3$,$^{15}N_2$, Primary Measurement Standard

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

Cerilliant Quality
ISO 17034
ISO/IEC 17025
ISO 13485
ISO 14001
ISO 9001

Product No.: U-013-1ML
Lot No.: FC12261802
Description of CRM: U-47700-$^{13}C_3$,$^{15}N_2$ in Methanol (Solution)
Retest Date: January 2022 See Section "Stability Assessment".
Storage: Store unopened in freezer (-10 °C to -25 °C).
Shipping: Ship cold. See Section "Stability Assessment".
Chemical formula: $C_{13}{}^{13}C_3H_{22}{}^{15}N_2OCl_2$
CAS No.: NA
Regulatory: USDEA Schedule I



Analyte	Certified Concentration ± 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

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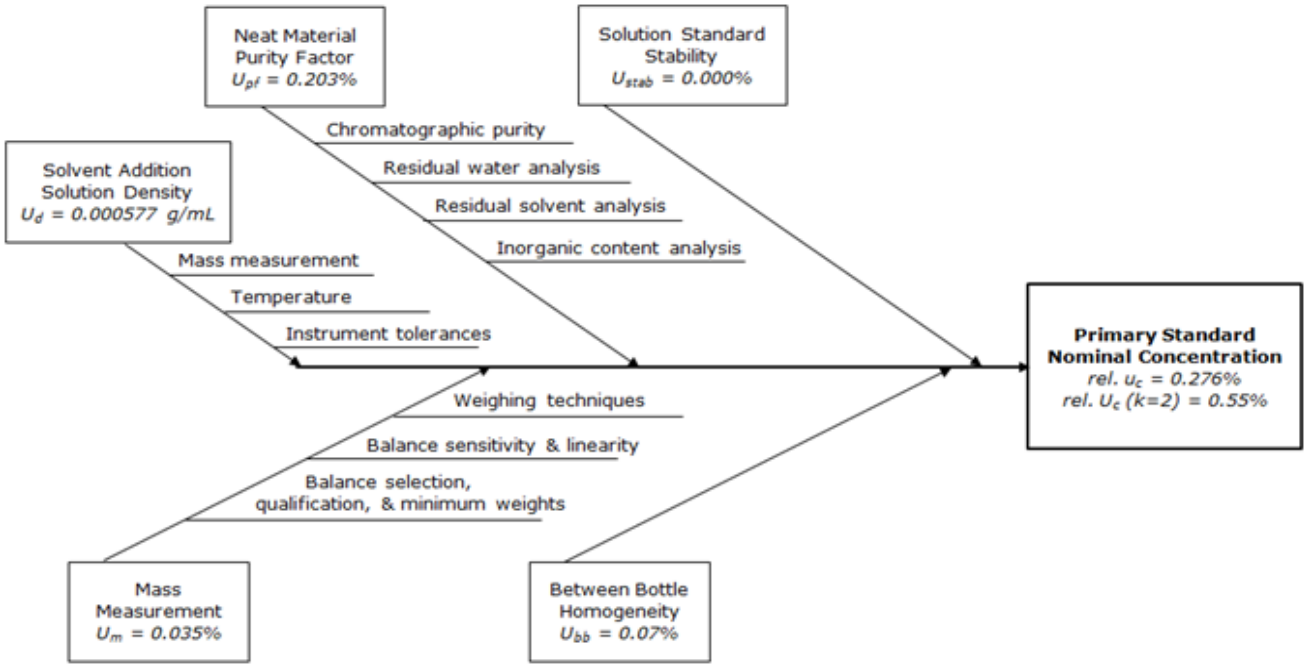
Packaging:	2 mL amber USP Type 1 glass ampoule containing not less than 1 mL of certified solution. Ampoules are overfilled to ensure a minimum of 1 mL volume can be transferred when using a 1mL Class A volumetric pipette.
Details on starting materials:	Each raw material utilized has been identified 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.



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Details on metrological traceability:

- This standard has been gravimetrically prepared using balances that have been fully qualified and calibrated to ISO 17025 requirements. All calibrations utilize NIST traceable weights which are calibrated externally by a qualified ISO 17025 accredited calibration laboratory to NIST standards. Qualification of each balance includes the assignment of a minimum weighing by a qualified and ISO 17025 accredited calibration vendor taking into consideration the balance and installed environmental conditions to ensure compliance with USP tolerances of NMT 0.10% relative error.
- Fill volume to predetermined specifications is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- The density and material Mass Balance Purity Factor of each raw material is traceable to the SI and higher order reference materials through mass measurement and instrument qualification and calibrations.

Details about certification process:

This standard has been prepared and certified under the ISO 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 (mg/mL)	**%RSD - Homogeneity**
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.

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Analyte Certification - Mass Balance Purity Factor

Each analyte is thoroughly identified and characterized using an orthogonal approach. A mass balance purity factor is assigned incorporating chromatographic purity and residual impurities. The mass balance purity factor is utilized to calculate the weighing adjustment necessary to ensure accuracy of the solution standard concentration.

Material Name:	U-47700-$^{13}C_3$,$^{15}N_2$	**Chemical Formula:**	$C_{13}{}^{13}C_3H_{22}{}^{15}N_2OCl_2$
Material Lot:	FC10111801	**CAS Number:**	NA
		Molecular Weight:	334.23

Material Characterization Summary

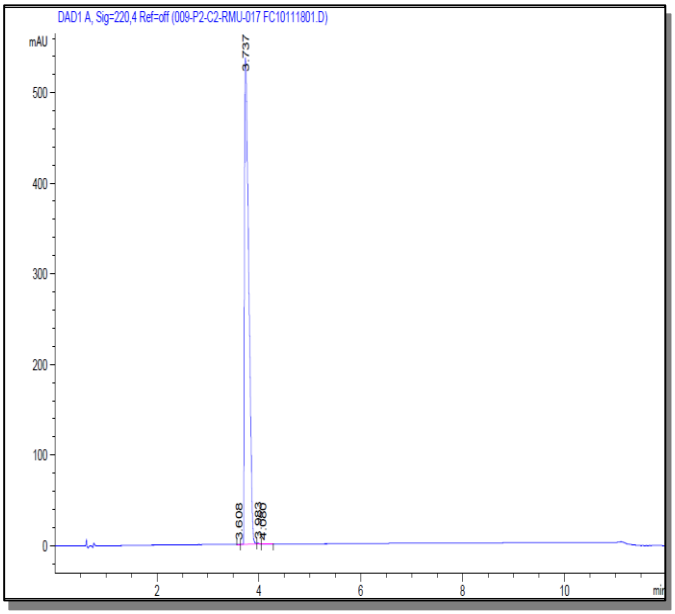
Analytical Test	**Method**	**Results**	
Primary Chromatographic Purity by HPLC/UV Analysis	SP10-0102	99.8%	
Secondary Chromatographic Purity by GC/FID Analysis	SP10-0101	99.8%	
Identity by LC/MS Analysis	SP10-0107	Consistent with Structure	
Isotopic Purity and Distribution by LC/MS SIM Analysis	SP10-0107	0.01% M_0 vs M_5	
		0.01% M_0 to M_2	2.61% M_4
		0.03% M_3	97.34% M_5
Identity by ^{1}H-NMR Analysis	USP <761>, SP10-0116	Consistent with Structure	
Residual Solvent Analysis by GC/FID Headspace	AM1087 [1]	None Detected	
Residual Water Analysis by Karl Fischer Coulometry	AM1346 [1]	Below Quantitation Limit	
Inorganic Content by Microash Analysis	SP10-0135	< 0.2%	
Mass Balance Purity Factor		99.79%	

[1] Validated analytical method.

- The primary chromatographic purity is calculated as the average of two independently performed analyses utilizing two different methods. Acceptance criteria requires the purity values to be within 0.5% of each other.
- The primary purity method was selected to optimize resolution of impurities while minimizing degradation of the analyte. Secondary purity methods with orthogonal detector capabilities from the primary purity method are used as controls to confirm an accurate purity value.
- The primary chromatographic purity value is used to calculate the Mass Balance Purity Factor.
- A secondary chromatographic purity method is utilized as a control.
- Mass Balance Purity Factor = [(100 - wt% residual solvent - wt% residual water - wt% residual inorganics) x Chromatographic Purity/100].
- Mass Balance Purity Factor does not include adjustment for chiral and/or isotopic purity.

Spectral and Physical Data

HPLC/UV



Column: Ascentis Express Phenyl-Hexyl, 2.7 µm, 3.0 x 100 mm

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

Gradient:

Time (min)	% A	% B
0.0	10	90
8.0	80	20
10.0	80	20
10.1	10	90

Flow Rate: 0.7 mL/min

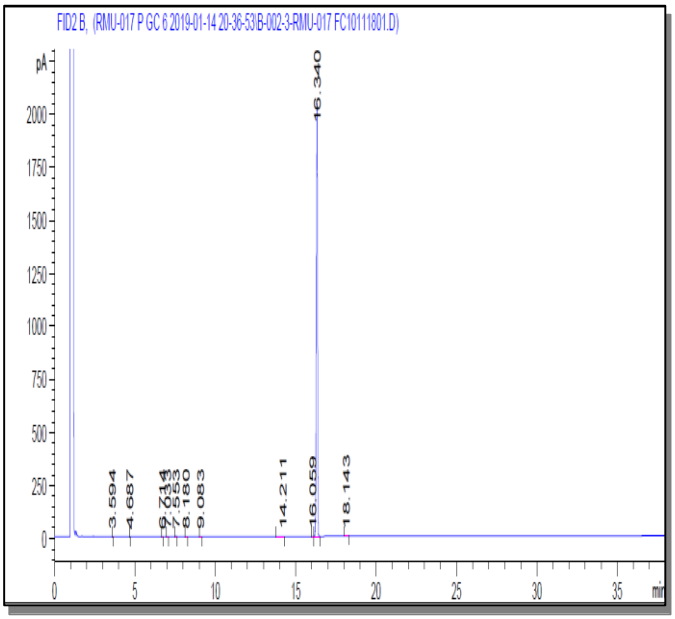
Wavelength: 220 nm

Sample Name: FC10111801

Acquired: January 14, 2019

Peak #	Ret Time	Area %
1	3.61	0.00
2	3.74	99.82
3	3.98	0.11
4	4.08	0.06

GC/FID



Column: DB-35ms, 30 m x 0.53 mm ID, 1.0 µm film thickness

Temp Program: 40°C to 200°C at 40°C/min
200°C to 280°C at 5°C/min hold 18 mir

Injector Temp: Cool-on-Column

Detector Temp: 325°C

Sample Name: FC10111801

Acquired: January 14, 2019

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
7	9.08	0.03
8	14.21	0.01
9	16.06	0.01
10	16.34	99.80
11	18.14	0.05

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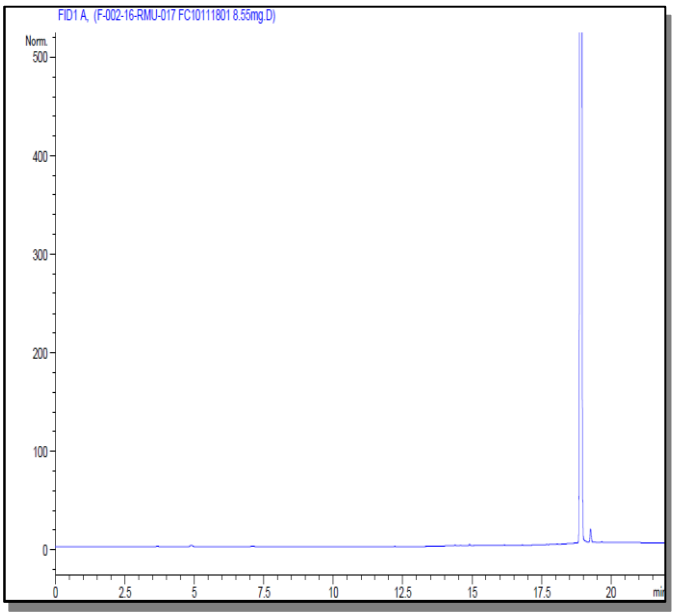
Spectral and Physical Data (cont.)

Residual Solvent Analysis by GC/FID Headspace



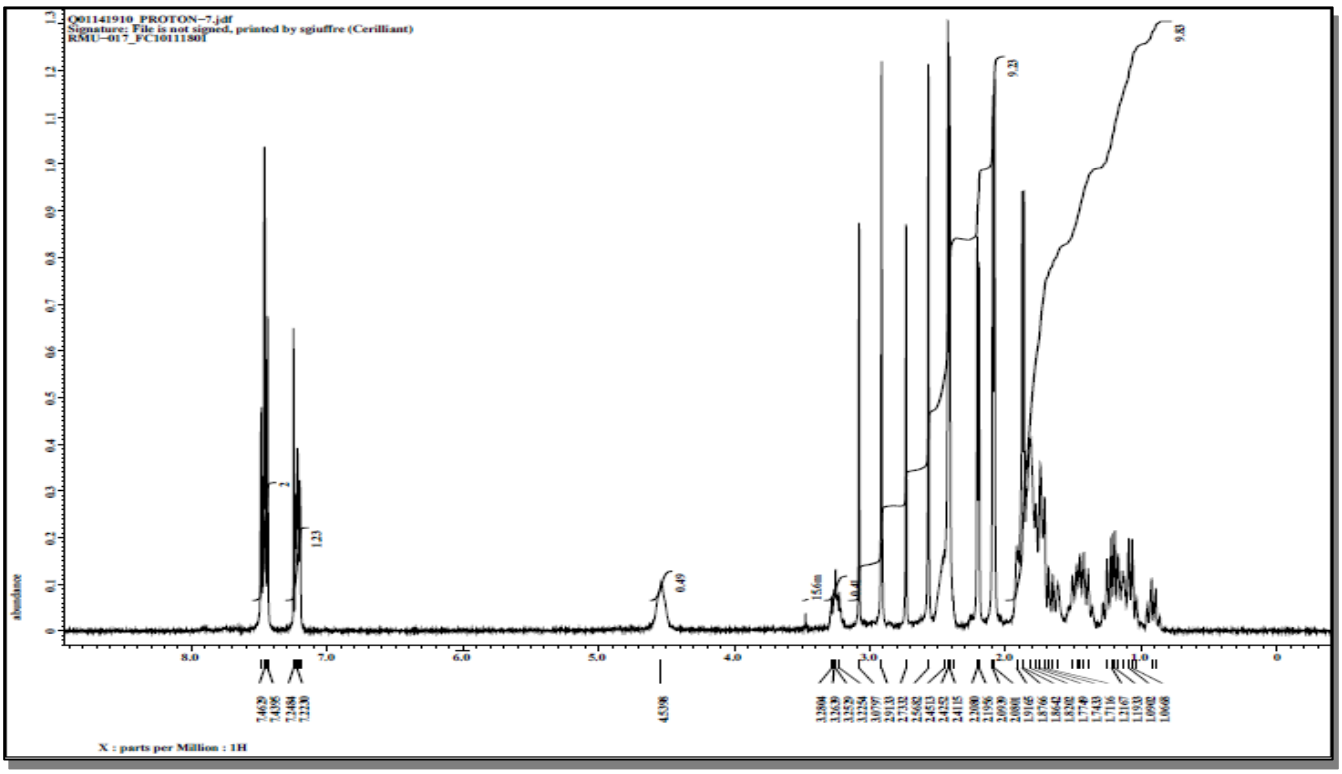
Column:	DB-ALC1 30 m x 0.53 mm, 3 µm film thickness
Temp Program:	40°C hold 12 min to 220°C at 40°C/min hold 5.5 min
Carrier Gas:	Helium
Flow Rate:	2.0 mL/min
Detector Heater Temp:	250°C
Injector:	Headspace Sampler
HS Oven Temp:	60°C
Vial Equilibration:	10 minutes
Sample Name:	FC10111801
Acquired:	January 15, 2019

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

ND - None Detected

^{1}H NMR

Instrument: JEOL ECS 400
Solvent: Chloroform-D



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Spectral and Physical Data (cont.)

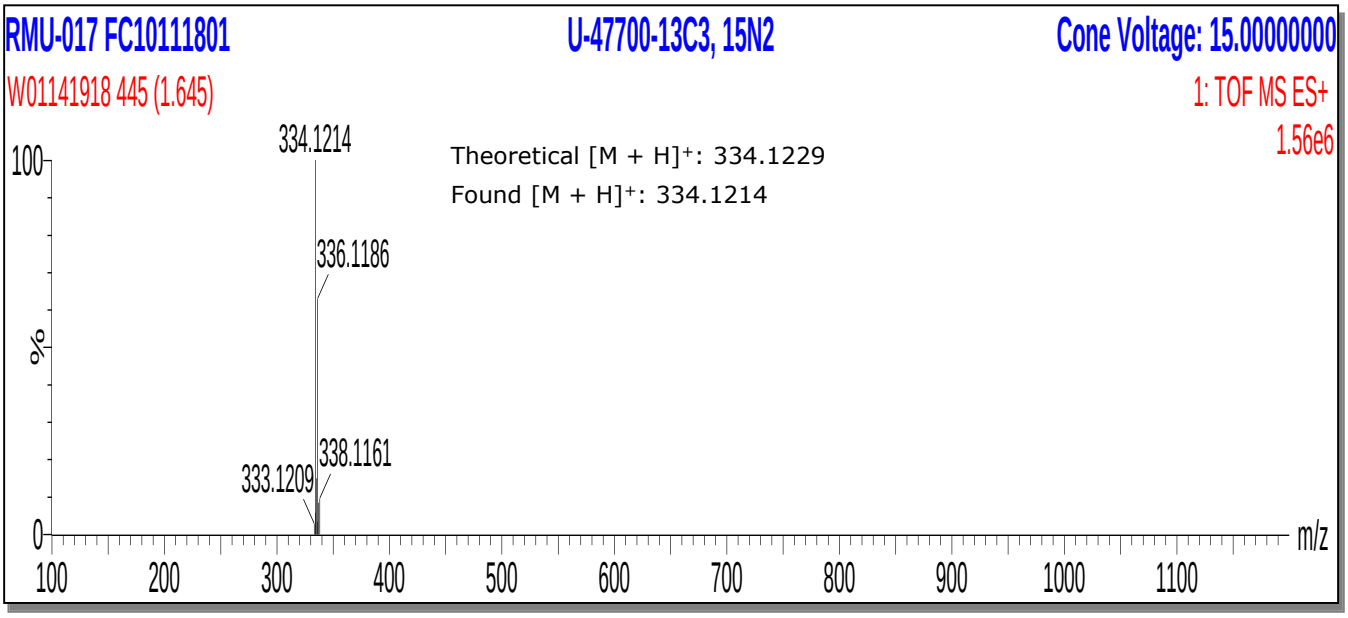
LC/MS

Column:	Ascentis Express C18, 2.7 µm, 3.0 x 50 mm	**Flow Rate:**	0.4 mL/min
Mobile Phase:	A: 0.1% Formic acid in Water	**Scan Range:**	100-1200 amu
	B: Acetonitrile	**Ionization:**	Electrospray, Positive Ion

Gradient:

Time (min)	% A	% B
0.0	80	20
0.5	80	20
4.0	20	80
5.8	20	80
6.0	80	20
8.0	80	20

Instrument: Waters XEVO G2 QTOF
Acquired: January 14, 2019



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Spectral and Physical Data (cont.)

Isotopic Purity by LC/MS SIM

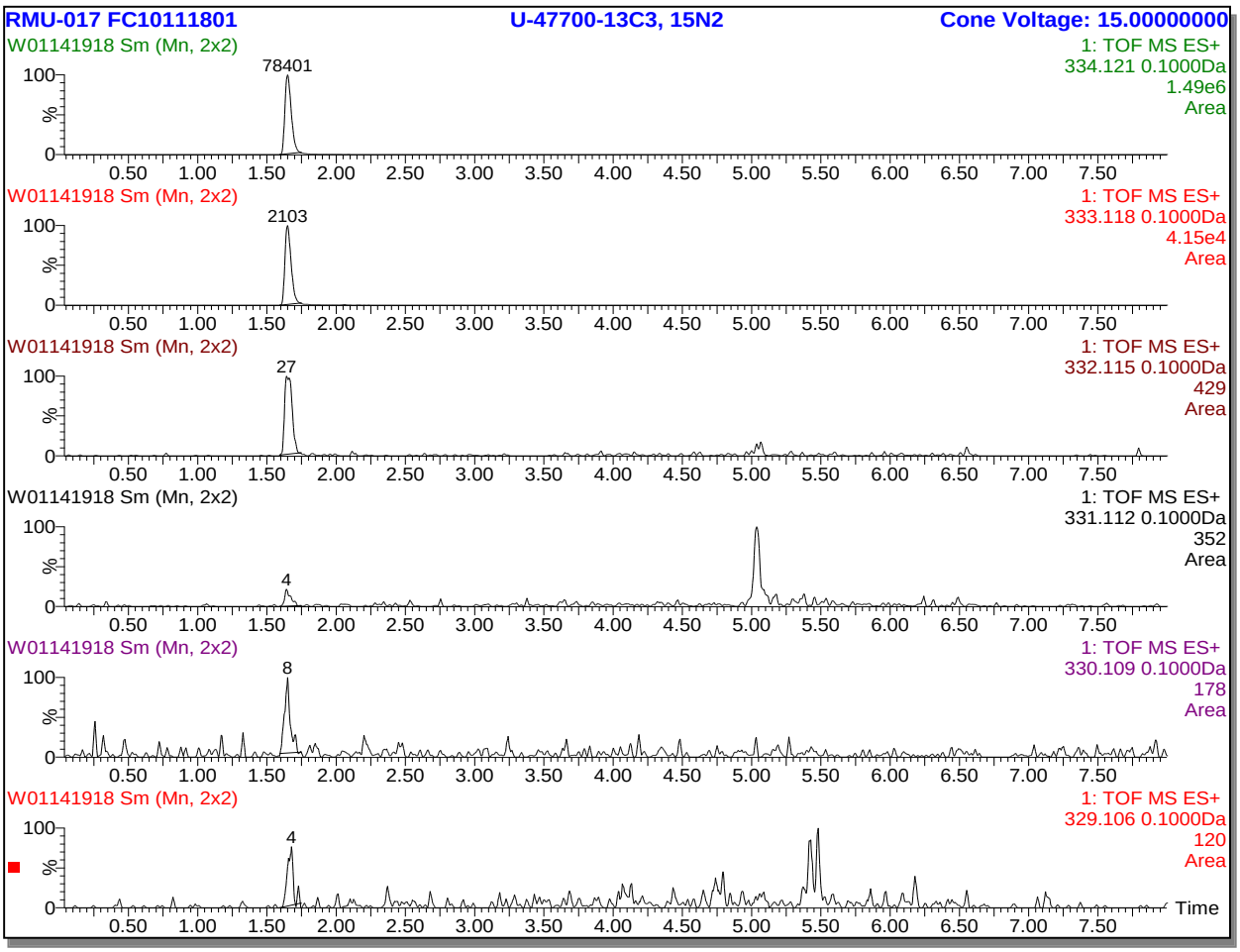
Column: Ascentis Express C18, 2.7 µm, 3.0 x 50 mm

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

Gradient:

Time (min)	% A	% B
0.0	80	20
0.5	80	20
4.0	20	80
5.8	20	80
6.0	80	20
8.0	80	20

Flow Rate: 0.4 mL/min
Scan Range: 329-334 amu
Ionization: Electrospray, Positive Ion
Instrument: Waters XEVO G2 QTOF
Acquired: January 14, 2019



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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 (U-003-1ML, U-47700) is listed below.*

Storage Condition	Mean Kinetic Temperature (MKT)	Time Period/Result
Freezer	-15°C	No decrease in purity was noted after four weeks.
Refrigerator	4°C	
Room Temperature	21°C	
40°C	40°C	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 31, 2020	Revised Retest Date from April 2020 to February 2021.
		Added Long Term Stability section.
02	February 02, 2021	Revised Retest Date from February 2021 to January 2022.

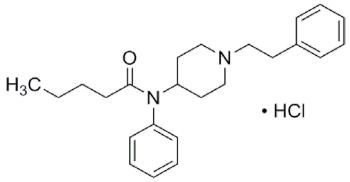
Certified Reference Material - Certificate of Analysis

Valeryl fentanyl, Primary Measurement Standard

N-Phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]-pentanamide HCl

Cerilliant Quality
ISO 17034
ISO/IEC 17025
ISO 13485
ISO 14001
ISO 9001

Product No.: V-074-1ML
Lot No.: FC12261805
Description of CRM: Valeryl fentanyl HCl in Methanol (Solution)
Nominal concentration is adjusted for HCl content.
Retest Date: February 2022 See Section "Stability Assessment".
Storage: Store unopened in freezer (-10 °C to -25 °C).
Shipping: Ambient. See Section "Stability Assessment".
Chemical formula: $C_{24}H_{32}N_2O \bullet HCl$
CAS No.: 117332-91-9
Regulatory: USDEA Schedule I



Analyte	Certified Concentration ± associated uncertainty U, u=k*u (k=2)
Valeryl 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.

ANAB ACCREDITED ISO 17034 REFERENCE MATERIAL PRODUCER

Darron Ellsworth, Quality Assurance Manager

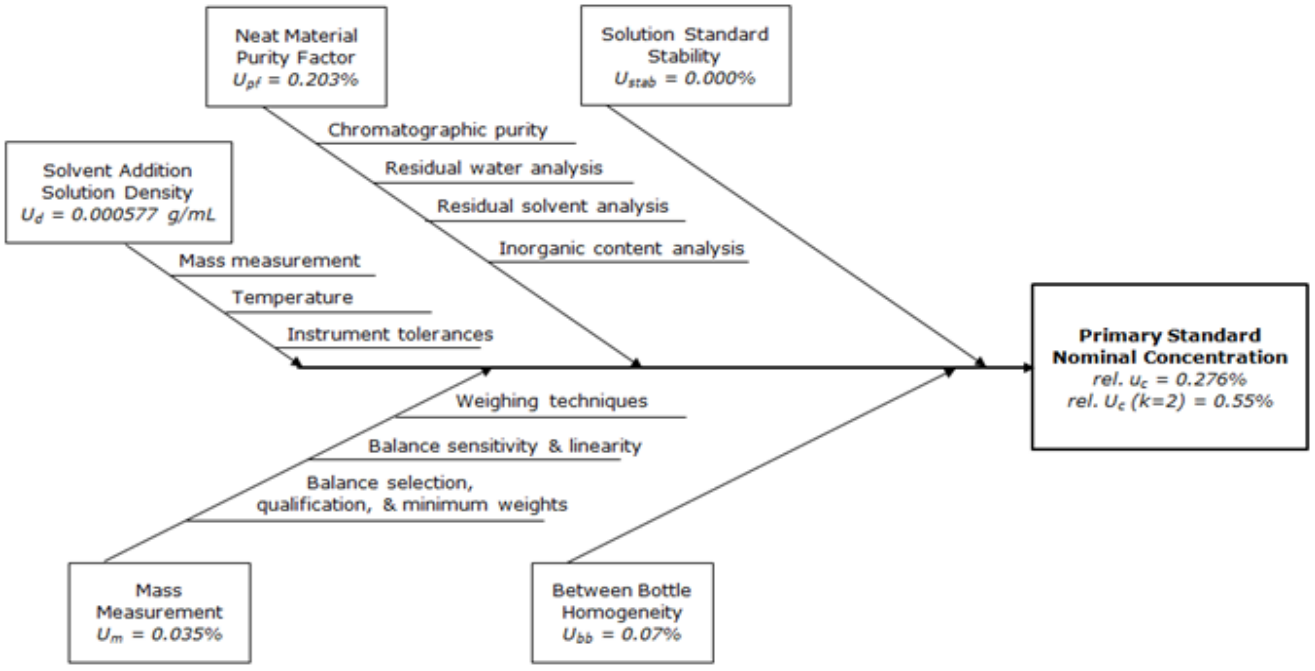
February 09, 2021
Issue Date

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.



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Details on metrological traceability:

- This standard has been gravimetrically prepared using balances that have been fully qualified and calibrated to ISO 17025 requirements. All calibrations utilize NIST traceable weights which are calibrated externally by a qualified ISO 17025 accredited calibration laboratory to NIST standards. Qualification of each balance includes the assignment of a minimum weighing by a qualified and ISO 17025 accredited calibration vendor taking into consideration the balance and installed environmental conditions to ensure compliance with USP tolerances of NMT 0.10% relative error.
- Fill volume to predetermined specifications is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- The density and material Mass Balance Purity Factor of each raw material is traceable to the SI and higher order reference materials through mass measurement and instrument qualification and calibrations.

Details about certification process:

This standard has been prepared and certified under the ISO 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.

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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 (mg/mL)	**%RSD - Homogeneity**
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.

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Analyte Certification - Mass Balance Purity Factor

Each analyte is thoroughly identified and characterized using an orthogonal approach. A mass balance purity factor is assigned incorporating chromatographic purity and residual impurities. The mass balance purity factor 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 Weight (base):**	364.52
Material Lot:	FC10031802	**Molecular Weight (salt):**	400.98
Chemical Formula:	$C_{24}H_{32}N_2O \bullet HCl$	**Salt Adjustment:**	1.100
CAS Number:	117332-91-9		

Material Characterization 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	99.4% [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 Microash Analysis	SP10-0135	< 0.2%		
Elemental Analysis	Outsourced		Calculated	Analyzed
		C	71.89%	71.83%
		H	8.30%	8.11%
		N	6.99%	7.26%
Mass Balance Purity Factor		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.

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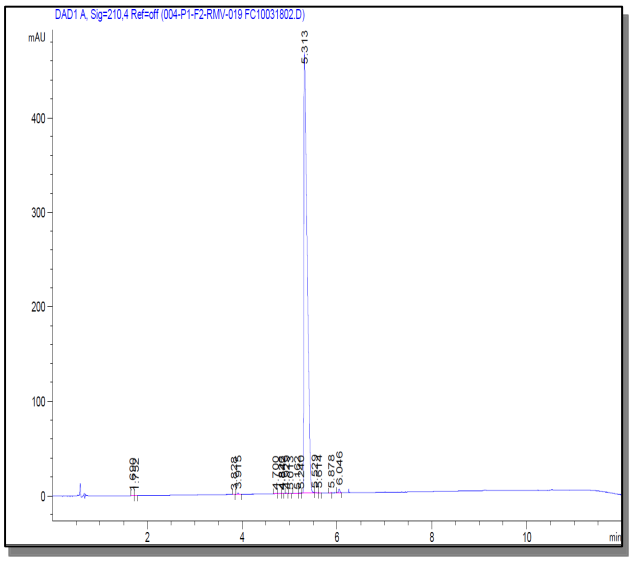
Spectral and Physical Data

HPLC/UV



Column: Ascentis Express C18, 2.7 µm, 3.0 x 100 mm

Mobile Phase: A: Acetonitrile
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/min

Wavelength: 210 nm

Sample Name: FC10031802

Acquired: February 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
7	4.84	0.01
8	4.93	0.03
9	5.01	0.01
10	5.16	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

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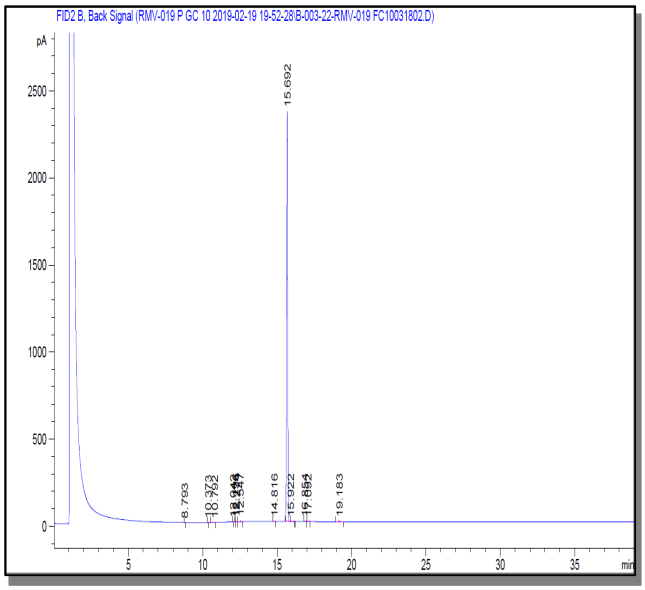
Spectral and Physical Data (cont.)

GC/FID



Column:	DB-35ms, 30 m x 0.53 mm ID, 1.0 µm film thickness
Temp Program:	60°C to 300°C at 20°C/min hold 27 min
Injector Temp:	Cool-on-Column
Detector Temp:	325°C
Sample Name:	FC10031802
Acquired:	February 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

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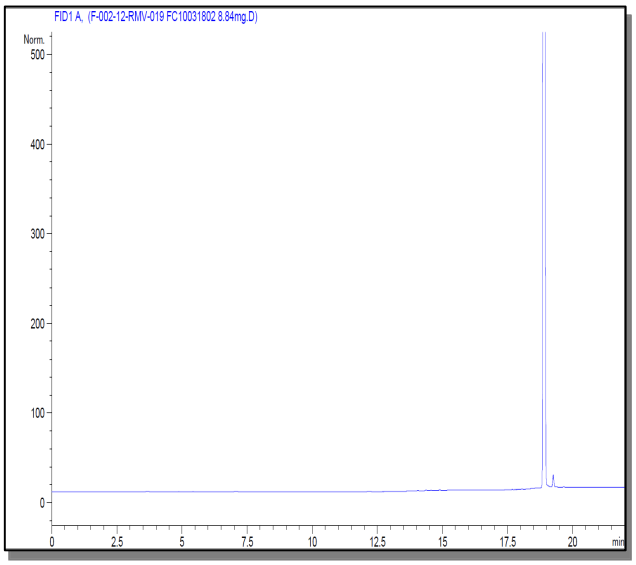
Spectral and Physical Data (cont.)

Residual Solvent Analysis by GC/FID Headspace



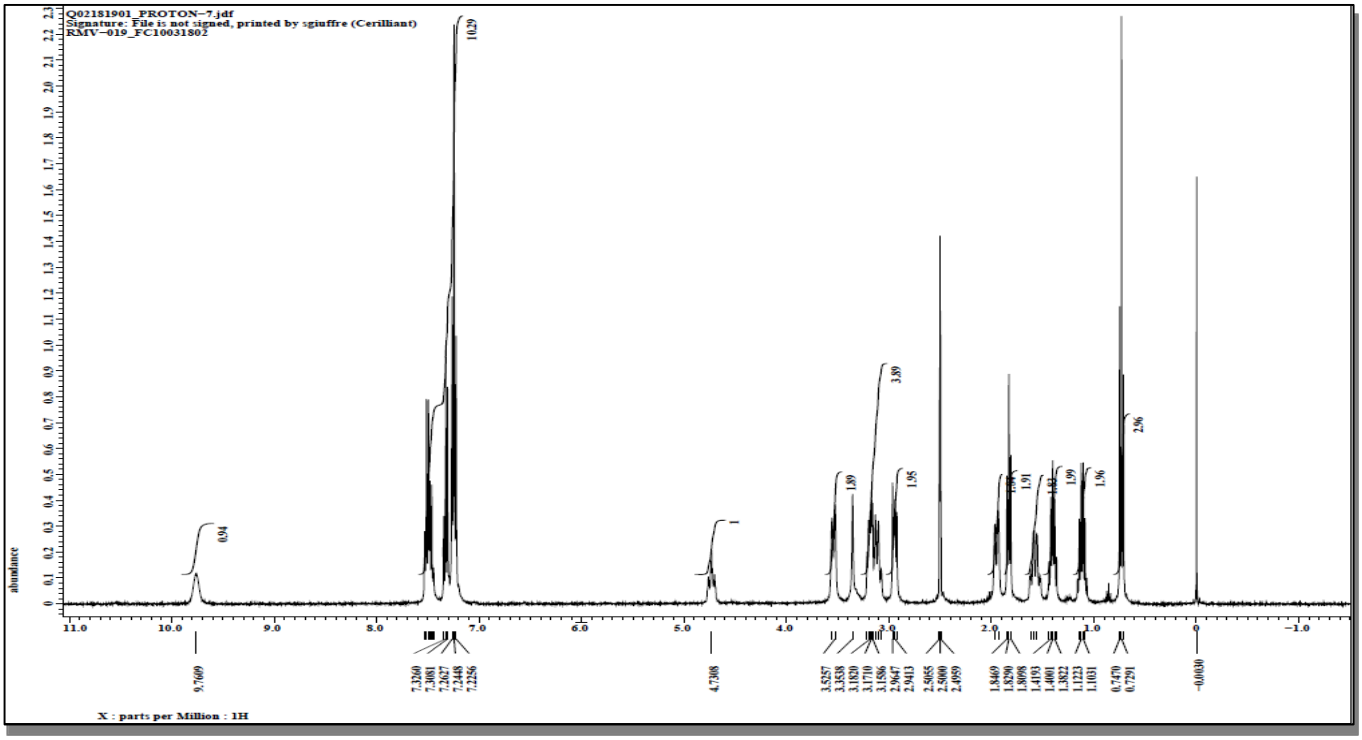
Column:	DB-ALC1 30 m x 0.53 mm, 3 µm film thickness
Temp Program:	40°C hold 12 min to 220°C at 40°C/min hold 5.5 min
Carrier Gas:	Helium
Flow Rate:	2.0 mL/min
Detector Heater Temp:	250°C
Injector:	Headspace Sampler
HS Oven Temp:	60°C
Vial Equilibration:	10 minutes
Sample Name:	FC10031802
Acquired:	February 26, 2019

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

ND- None Detected

^{1}H NMR

Instrument: JEOL ECS 400
Solvent: DMSO-D_6



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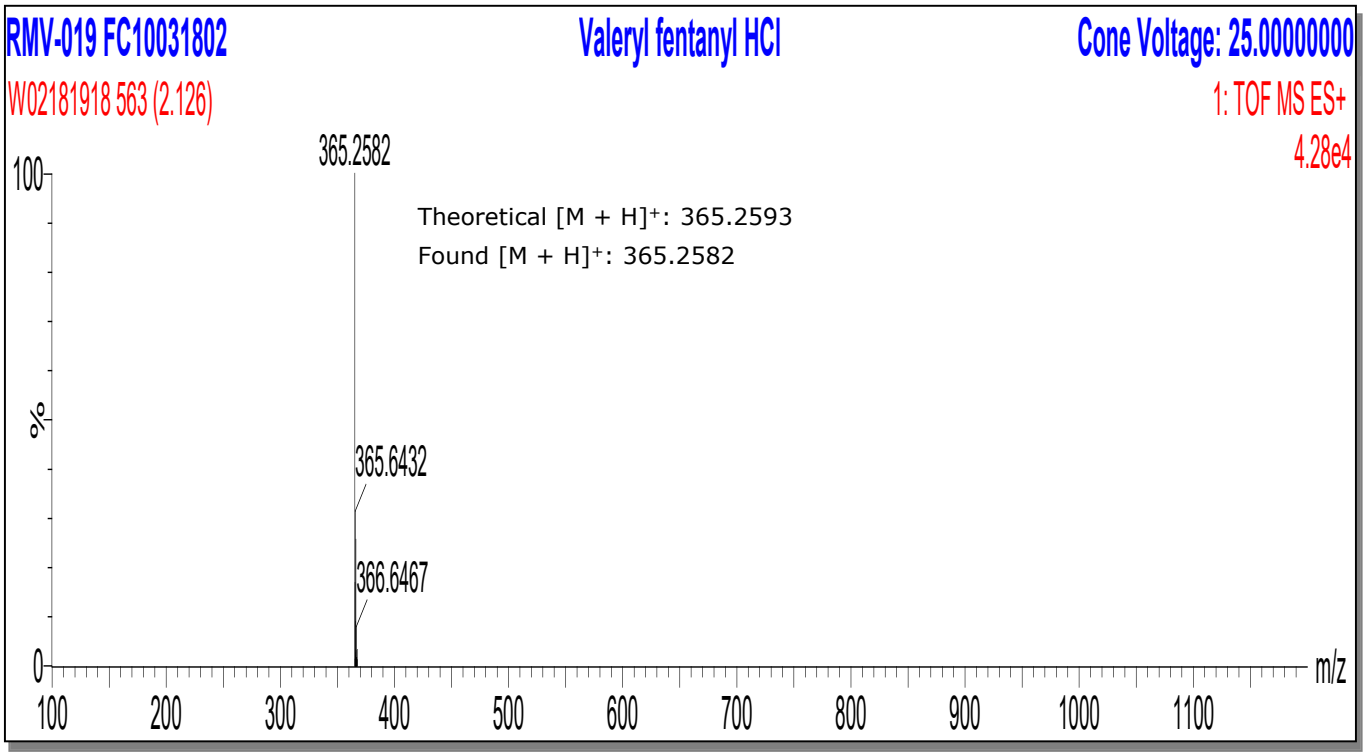
Spectral and Physical Data (cont.)

LC/MS

Column:	Ascentis Express C18, 2.7 µm, 3.0 x 50 mm	**Flow Rate:**	0.4 mL/min
Mobile Phase:	A: 0.1% Formic acid in Water B: Acetonitrile	**Scan Range:**	100-1200 amu
		Ionization:	Electrospray, Positive Ion
		Instrument:	Waters XEVO G2 QTOF
Gradient:		**Acquired:**	February 18, 2019

Time (min)	% A	% B
0.0	80	20
0.5	80	20
4.0	20	80
5.8	20	80
6.0	80	20
8.0	80	20



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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 this product is listed below.*

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

Transport/Shipping: *Stability studies support the transport of this product at ambient conditions.*

Long Term Stability: *Long term stability has been assessed for Freezer storage (-10 °C to -25 °C) conditions. Stability of a minimum of 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.
02	February 09, 2021	Updated Retest Date of February 2021 to February 2022.
		Updated page reference on first page.

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

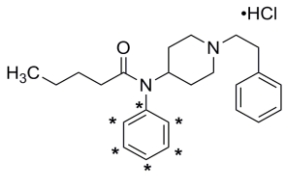
Certified Reference Material - Certificate of Analysis

Valeryl fentanyl-$^{13}C_6$, Primary Measurement Standard

N-Phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]-pentanamide-$^{13}C_6$ HCl

Cerilliant Quality
ISO 17034
ISO/IEC 17025
ISO 13485
ISO 14001
ISO 9001

Product No.: V-075-1ML
Lot No.: FC12261808
Description of CRM: Valeryl fentanyl-$^{13}C_6$ HCl in Methanol (Solution)
Nominal concentration is adjusted for HCl content.
Retest Date: November 2021 See Section "Stability Assessment".
Storage: Store unopened in freezer (-10 °C to -25 °C).
Shipping: Ambient. See Section "Stability Assessment".
Chemical formula: $C_{18}{}^{13}C_6H_{32}N_2O \bullet HCl$
CAS No.: NA
Regulatory: USDEA Schedule I



Analyte	Certified Concentration ± associated uncertainty U, u=k*u (k=2)
Valeryl 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 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.

ANAB ACCREDITED ISO 17034 REFERENCE MATERIAL PRODUCER

Darron Ellsworth, Quality Assurance Manager

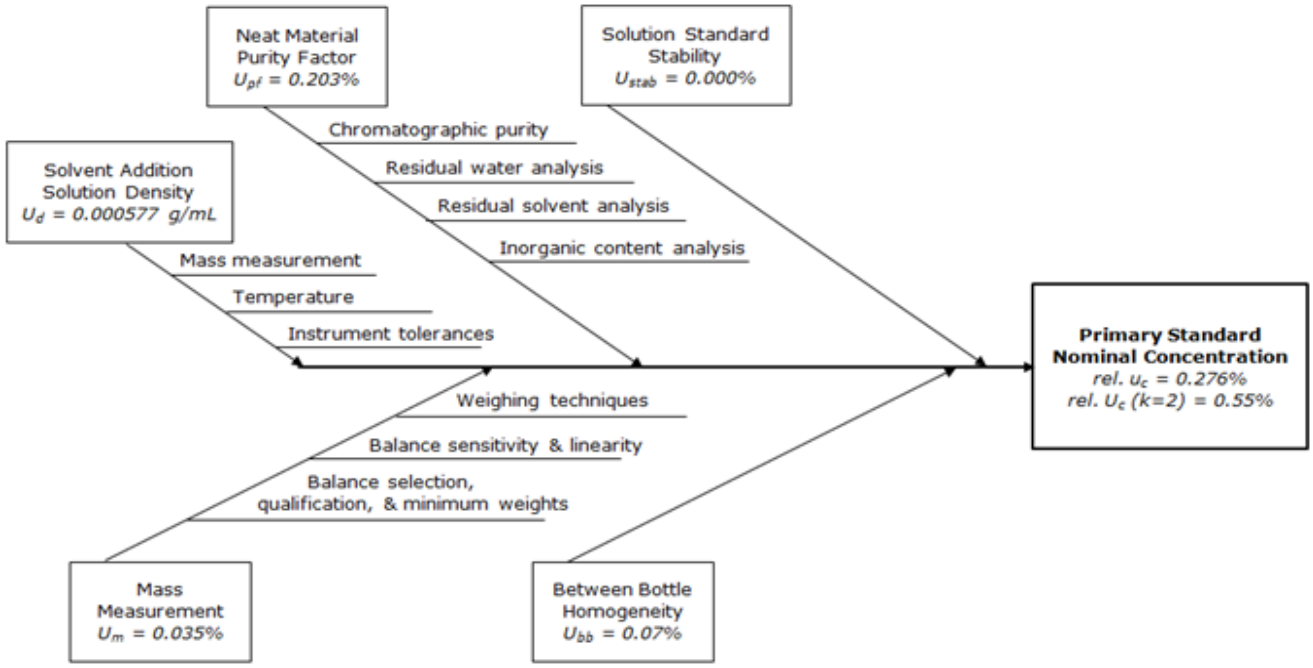
January 07, 2021
Issue Date

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.



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Details on metrological traceability:

- This standard has been gravimetrically prepared using balances that have been fully qualified and calibrated to ISO 17025 requirements. All calibrations utilize NIST traceable weights which are calibrated externally by a qualified ISO 17025 accredited calibration laboratory to NIST standards. Qualification of each balance includes the assignment of a minimum weighing by a qualified and ISO 17025 accredited calibration vendor taking into consideration the balance and installed environmental conditions to ensure compliance with USP tolerances of NMT 0.10% relative error.
- Fill volume to predetermined specifications is gravimetrically verified throughout the dispensing process using qualified and calibrated balances.
- The density and material Mass Balance Purity Factor of each raw material is traceable to the SI and higher order reference materials through mass measurement and instrument qualification and calibrations.

Details about certification process:

This standard has been prepared and certified under the ISO 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**
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:	Valeryl fentanyl-$^{13}C_6$ HCl	**Molecular Weight (base):**	370.48
Material Lot:	FC10031805	**Molecular Weight (salt):**	406.94
Chemical Formula:	$C_{18}{}^{13}C_6H_{32}N_2O \bullet HCl$	**Salt Adjustment:**	1.098
CAS Number:	NA		

Material Characterization Summary

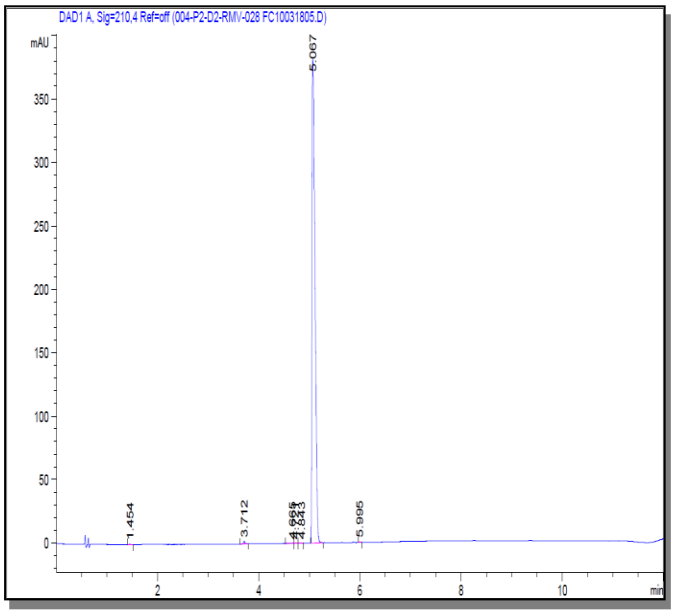
Analytical Test	**Method**	**Results**		
Primary Chromatographic Purity by HPLC/UV Analysis	SP10-0102	99.5%		
Secondary Chromatographic Purity by GC/FID Analysis	SP10-0101	99.5%		
Identity by LC/MS Analysis	SP10-0107	Consistent with Structure		
Isotopic Purity and Distribution by LC/MS Analysis	SP10-0107	0.01% $^{13}C_0$ vs $^{13}C_6$		
		0.01% $^{13}C_0$	2.08% $^{13}C_5$	
		0.00% $^{13}C_1$ to $^{13}C_3$	97.90% $^{13}C_6$	
		0.01% $^{13}C_4$		
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 Coulometry	AM1346 [1]	Below Quantitation Limit		
Elemental Analysis	Outsourced		Calculated	Analyzed
		C	53.13%	70.69%
		H	8.17%	8.07%
		N	6.88%	7.07%
Inorganic Content by Microash Analysis	SP10-0135	< 0.2%		
Mass Balance Purity Factor		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

HPLC/UV



Column: Ascentis Express C18, 2.7 µm, 3.0 x 100 mm

Mobile Phase: A: Acetonitrile
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/min

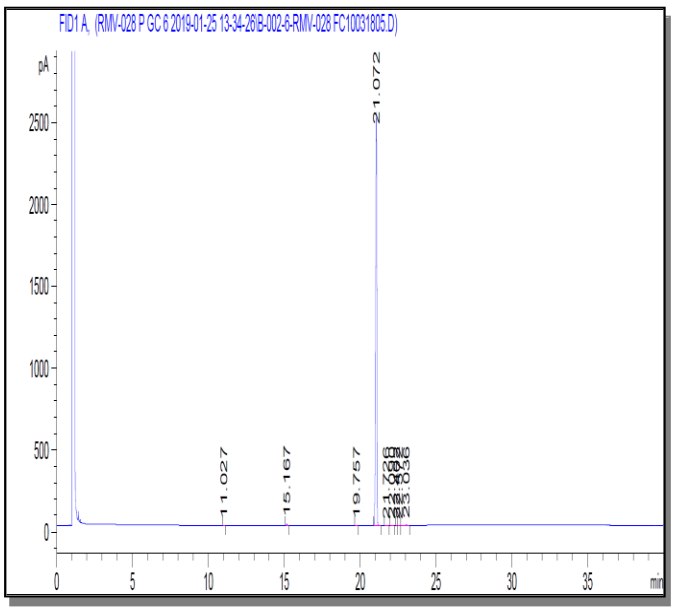
Wavelength: 210 nm

Sample Name: FC10031805

Acquired: January 22, 2019

Peak #	Ret Time	Area %
1	1.45	0.03
2	3.71	0.23
3	4.67	0.04
4	4.72	0.03
5	4.84	0.02
6	5.07	99.59
7	6.00	0.06

GC/FID



Column: DB-5ms, 30 m x 0.53 mm ID, 1.5 µm film thickness

Temp Program: 40°C to 200°C at 40°C/min
200°C to 300°C at 5°C/min
hold 16 min

Injector Temp: Cool-on-Column

Detector Temp: 325°C

Sample Name: FC10031805

Acquired: January 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
7	22.40	0.01
8	22.57	0.01
9	23.04	0.06

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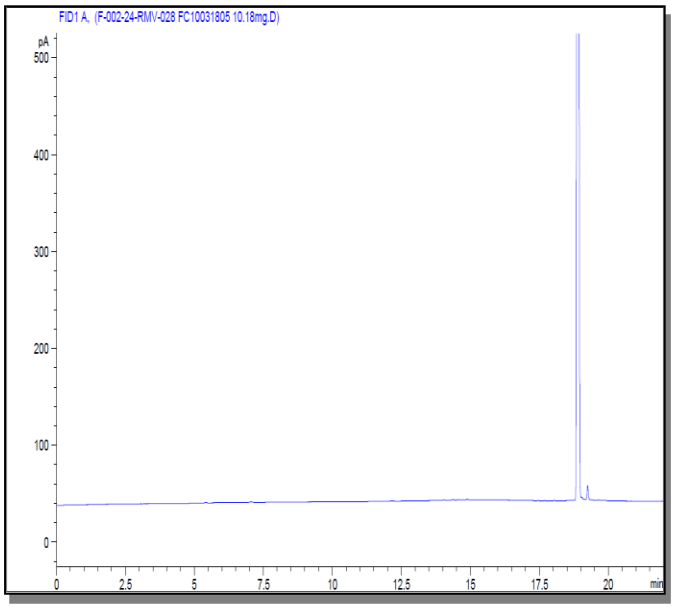
Spectral and Physical Data (cont.)

Residual Solvent Analysis by GC/FID Headspace



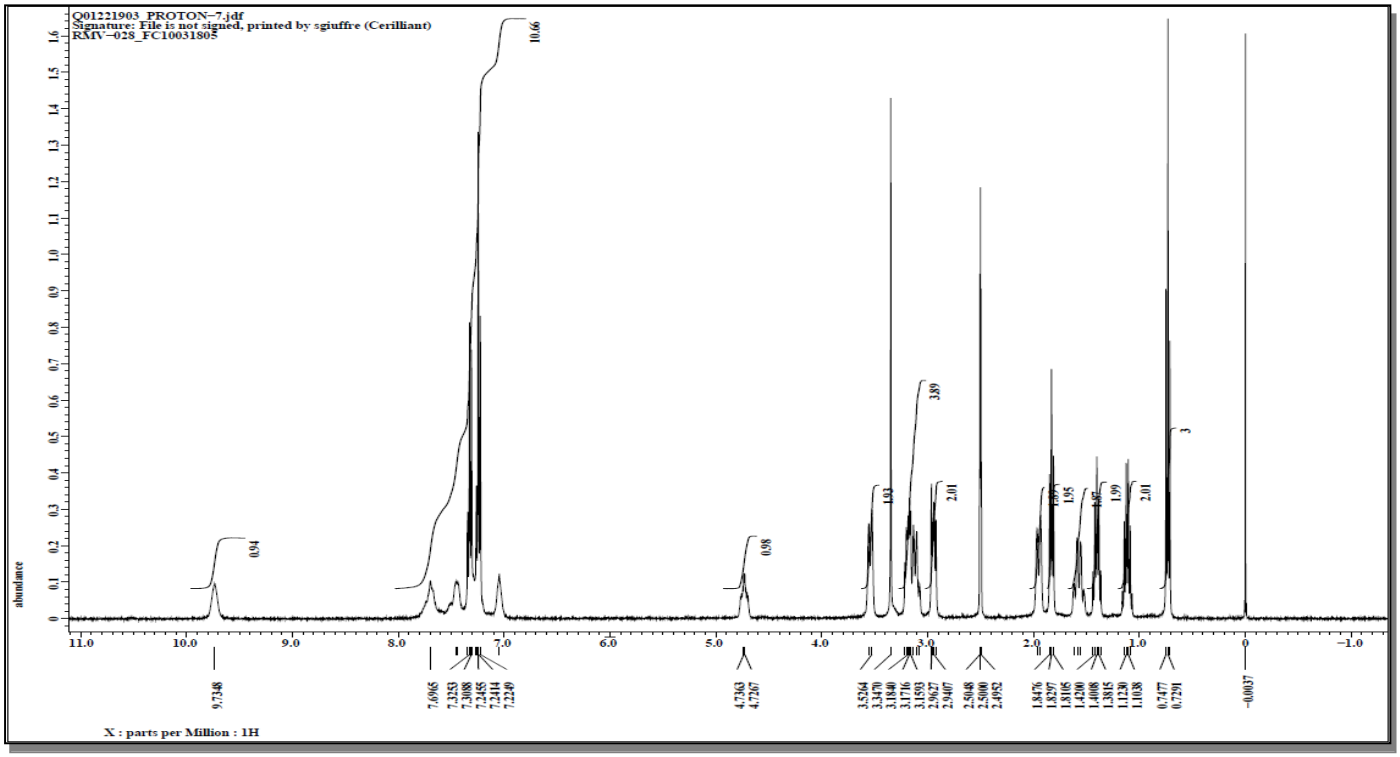
Column:	DB-ALC1 30 m x 0.53 mm, 3 µm film thickness
Temp Program:	40°C hold 12 min to 220°C at 40°C/min hold 5.5 min
Carrier Gas:	Helium
Flow Rate:	2.0 mL/min
Detector Heater Temp:	250°C
Injector:	Headspace Sampler
HS Oven Temp:	60°C
Vial Equilibration:	10 minutes
Sample Name:	FC10031805
Acquired:	January 23, 2019

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

ND - None Detected

^{1}H NMR

Instrument: JEOL ECS 400
Solvent: DMSO-D_6



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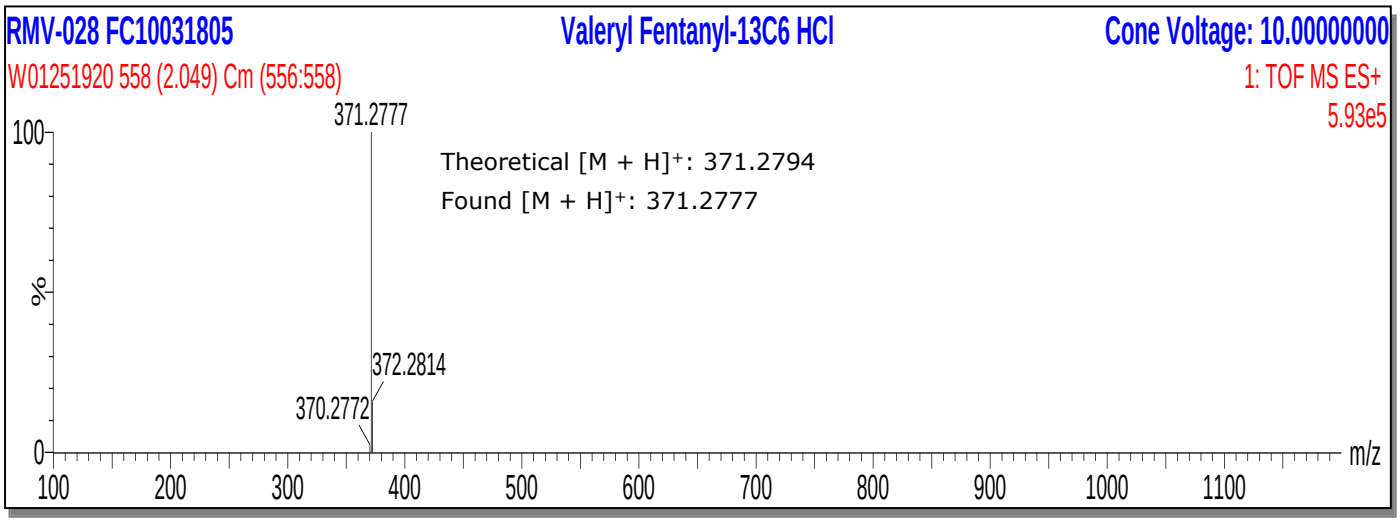
Spectral and Physical Data (cont.)

LC/MS

Column:	Ascentis Express C18, 2.7 µm, 3.0 x 50 mm	**Flow Rate:**	0.4 mL/min
Mobile Phase:	A: 0.1% Formic acid in Water B: Acetonitrile	**Scan Range:**	100-1200 amu
		Ionization:	Electrospray, Positive Ion
		Instrument:	Waters XEVO G2 QTOF
Gradient:		**Acquired:**	January 25, 2019

Time (min)	% A	% B
0.0	80	20
0.5	80	20
4.0	20	80
5.8	20	80
6.0	80	20
8.0	80	20



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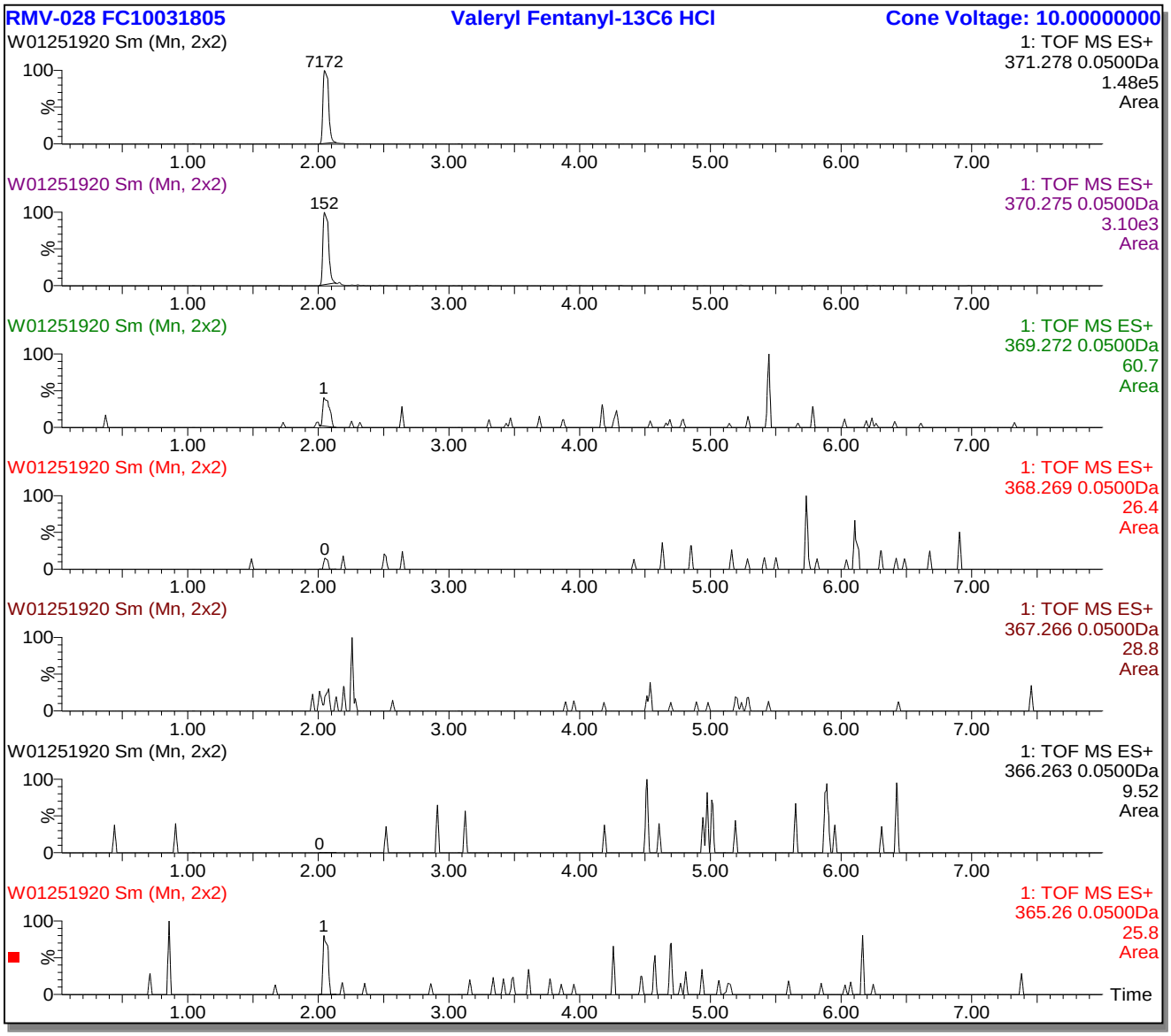
Spectral and Physical Data (cont.)

Isotopic Purity by LC/MS SIM

Column: Ascentis Express C18, 2.7 µm, 3.0 x 50 mm
Mobile Phase: A: 0.1% Formic acid in Water
B: Acetonitrile
Gradient:

Time (min)	% A	% B
0.0	80	20
0.5	80	20
4.0	20	80
5.8	20	80
6.0	80	20
8.0	80	20

Flow Rate: 0.4 mL/min
Scan Range: 365-371 amu
Ionization: Electrospray, Positive Ion
Instrument: Waters XEVO G2 QTOF
Acquired: January 25, 2019



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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	No decrease in purity was noted after four weeks.
Refrigerator	4°C	
Room Temperature	21°C	
40°C	40°C	

Transport/Shipping: *Stability studies support the transport of this product at ambient conditions.*

Long Term Stability: *Long term stability has been assessed for Freezer storage (-10 °C to -25 °C) conditions. Stability of a minimum of 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.