

Potency Claims - only as Accurate as your Reference Material

Challenges with unstable THC
and related Cannabinoids

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Cerilliant Corporation

Why is accuracy of potency assignment is important?

Various biomarkers are naturally at low levels, even with enhanced strains

- Safety & efficacy
- Legal & regulatory requirements

Safety & patient care

- Reduce risks associated with variable dosage - recent studies have highlighted potential dangers associated with *Cannabis* dosage
 - In studies treating depression, *Cannabis* has shown therapeutic efficacy at low doses, but in high doses THC can worsen symptoms of depression and other psychiatric conditions like psychosis.¹
 - Epidemiologic research suggests that *Cannabis* may have a dose-dependent influence on seizure threshold, provoking and prolonging seizures at certain doses in adults and children with epilepsy.^{2,3}
 - Marijuana use can increase convulsant effects in animal epilepsy models and in a case study, marijuana use was implicated as the cause of new-onset seizures.⁴
- Accuracy of Cannabis profiling and potency testing using accurate Certified Reference Materials (CRMs) is therefore critical to ensuring safe and successful patient outcomes when using Cannabis-based medicines.⁵

1. <http://www.sciencedaily.com/releases/2007/10/071023183937.htm>

2. <http://dx.doi.org/10.1016/j.yebeh.2014.08.135>

3. www.ncbi.nlm.nih.gov/pubmed/11737161

4. <http://onlinelibrary.wiley.com/doi/10.1046/j.1528-1157.2001.19301.x/full>

5. www.canorml.org/RingTestOShaughnessys_Aut11.pdf

Legal & regulatory requirements

- Legal requirements for classifying a strain are tight; inconsistencies in raw material and reference material lots could be critical
 - The state of Colorado requires *Cannabis* retailers to provide a cannabinoid potency profile for *Cannabis*-derived products.¹
 - District of Columbia requires listing the cannabinoid profile of the marijuana contained within, including the THC level.²
 - European pharmaceutical companies that manufacture *Cannabis*-based medicines must conform to botanical raw material specifications that include tests for identification, impurities, and extraneous matter as well as assays for acidic and neutral cannabinoids.^{3,4}
 - Cannabinoid profile; amount per package; amount per patient

1. <http://www.sos.state.co.us/CCR/GenerateRulePdf.do?ruleVersionId=5890&fileName=1%20CCR%20212-2>

2. Comparison of Marijuana Laws- medicinal use-FINAL

3. *Cannabis-med.org/data/pdf/2003-02-4_0.pdf*

4. Mechoulam, R.: *Cannabinoids as Therapeutics*, Birkhäuser 2005

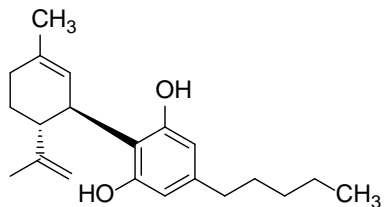
Results are only as accurate as the reference!

- Reference materials play a critical role in assuring quality of medicines and supplements
- Accuracy and reliability of analytical results is dependent on accuracy and reliability of the method of analysis, accuracy in the preparation of samples, and accuracy of the calibrators used
- Highly pure, well-characterized, reference materials are critical to the accuracy of the analysis
- Design, preparation, packaging, and storage of reference materials affect traceability, accuracy of concentration, stability, and uncertainty

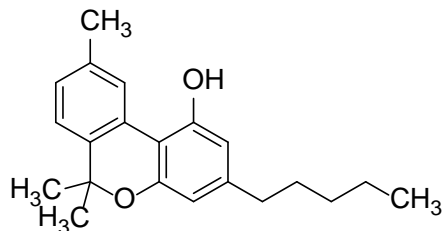
What makes a good Reference Material?

One suitable for quantitative applications?

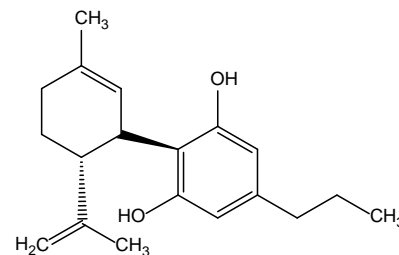
- ✓ High purity thoroughly & accurately characterized components – neat material characterization
- ✓ Solution standard design – whether pre-prepared or prepared at the bench
 - ✓ Prepared using accurate, calibrated, and qualified balances (pipettes & glassware when needed)
 - ✓ Accurate weighing operation and solvent addition
 - ✓ Traceability of all components
 - ✓ High purity diluents and/or stabilizers, compatible with the compound(s) and method
 - ✓ Analyzed to verify accuracy & consistency
 - ✓ Appropriate packaging and storage
 - ✓ Assessment of shelf life



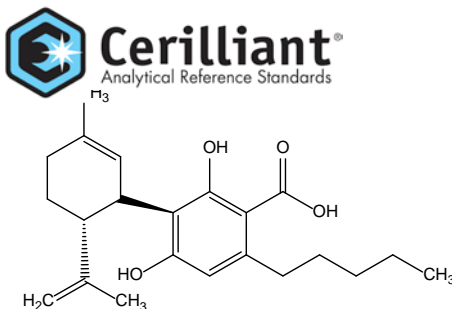
Cannabidiol



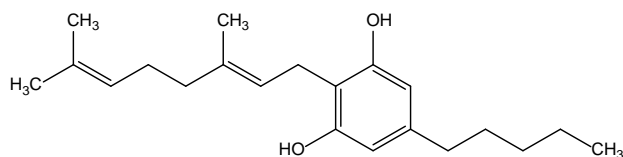
Cannabinol



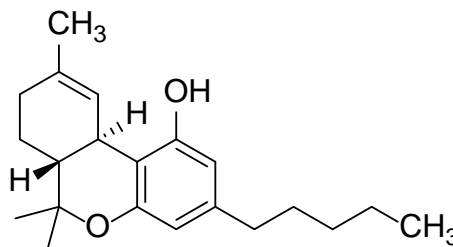
Cannabidivarin (CBDV)



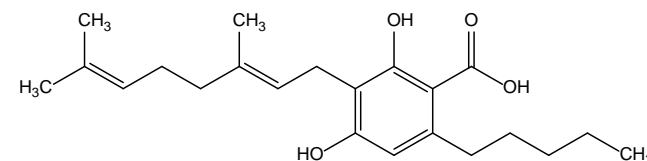
Cannabidiolic acid (CBDA)



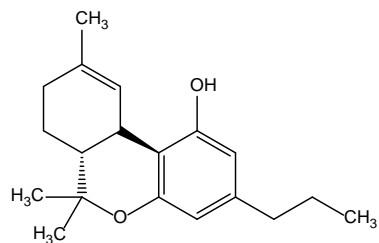
Cannabigerol (CBG)



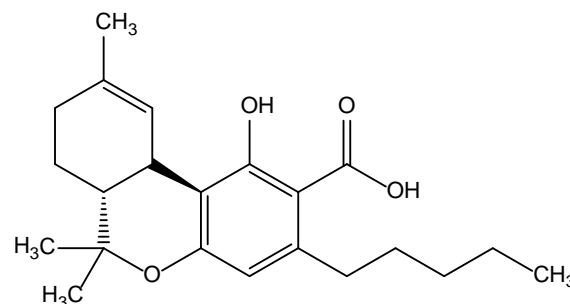
(-)- Δ^9 -THC



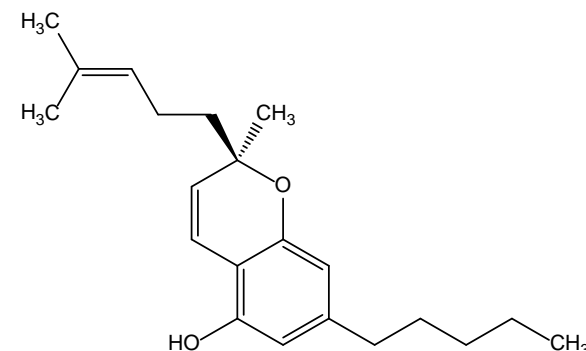
Cannabigerolic acid (CBGA)



Tetrahydrocannabivarin (THCV)



Δ^9 -Tetrahydrocannabinolic acid A (THCA-A)



Cannabichromene (CBC)

Most commonly monitored *Cannabis* cannabinoid biomarkers

Reference materials – two options:

Reference Solution Prepared from Neat Starting Material – Typical Approach

- Volumetric solutions are prepared by weighing neat materials, diluting and assessing stability in volumetric flask
- Accurate preparation requires certification of the equipment, QC
- Requires special handling of toxic, potent, or hazardous materials
- Hygroscopic, volatile, or difficult to handle materials affect repeatability and accuracy
- Weighing small amounts accurately is time-consuming and costly (Lilly 45 minutes per vial)
- Solutions may not be stable over time due to changes in concentration and degradation

Some Cannabis biomarkers require dilution immediately upon isolation including:

- Δ^9 -THC
- THCV
- CBC
- CBDA
- THCAA

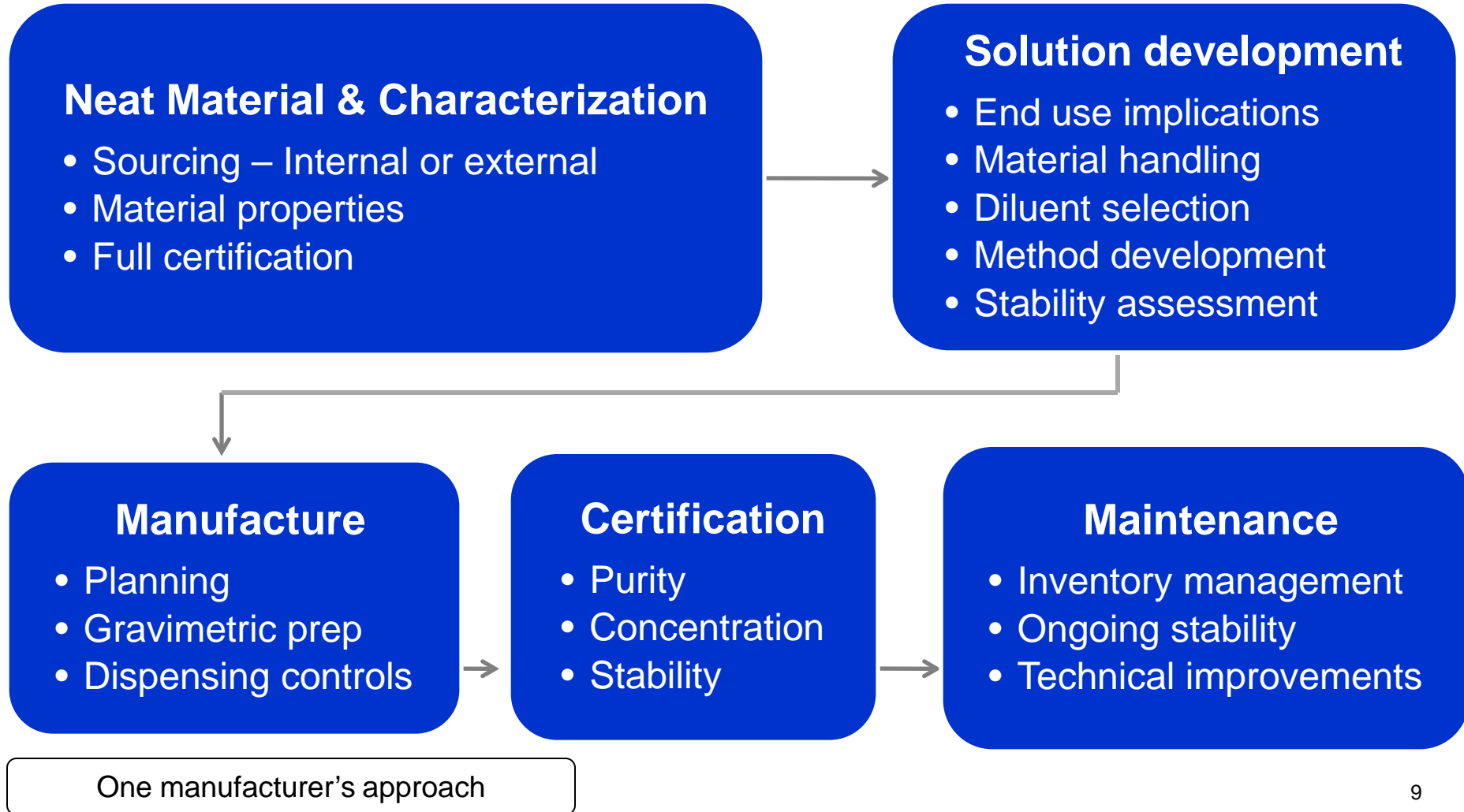


Ampouled Certified Solution Standards

- Spiked directly into diluent for calibrators or controls
Quantitatively transferred without dilution for analysis
Pre-prepared dilute solution provides safety in handling of toxic, potent, or hazardous materials in the analytical lab
Provides labor savings by eliminating weighing operations and providing consistency of analysis by eliminating variability of the reference – particularly for difficult to handle materials
Format (inert atmosphere) promotes long term stability
Fully certified with uncertainty & traceability established
DEA & Health Canada exemptions eliminate regulatory burden for laboratory
- Widely used in clinical/forensic toxicology & environmental industries



Proper design & preparation necessary to ensure stability & accuracy



Neat materials - certification

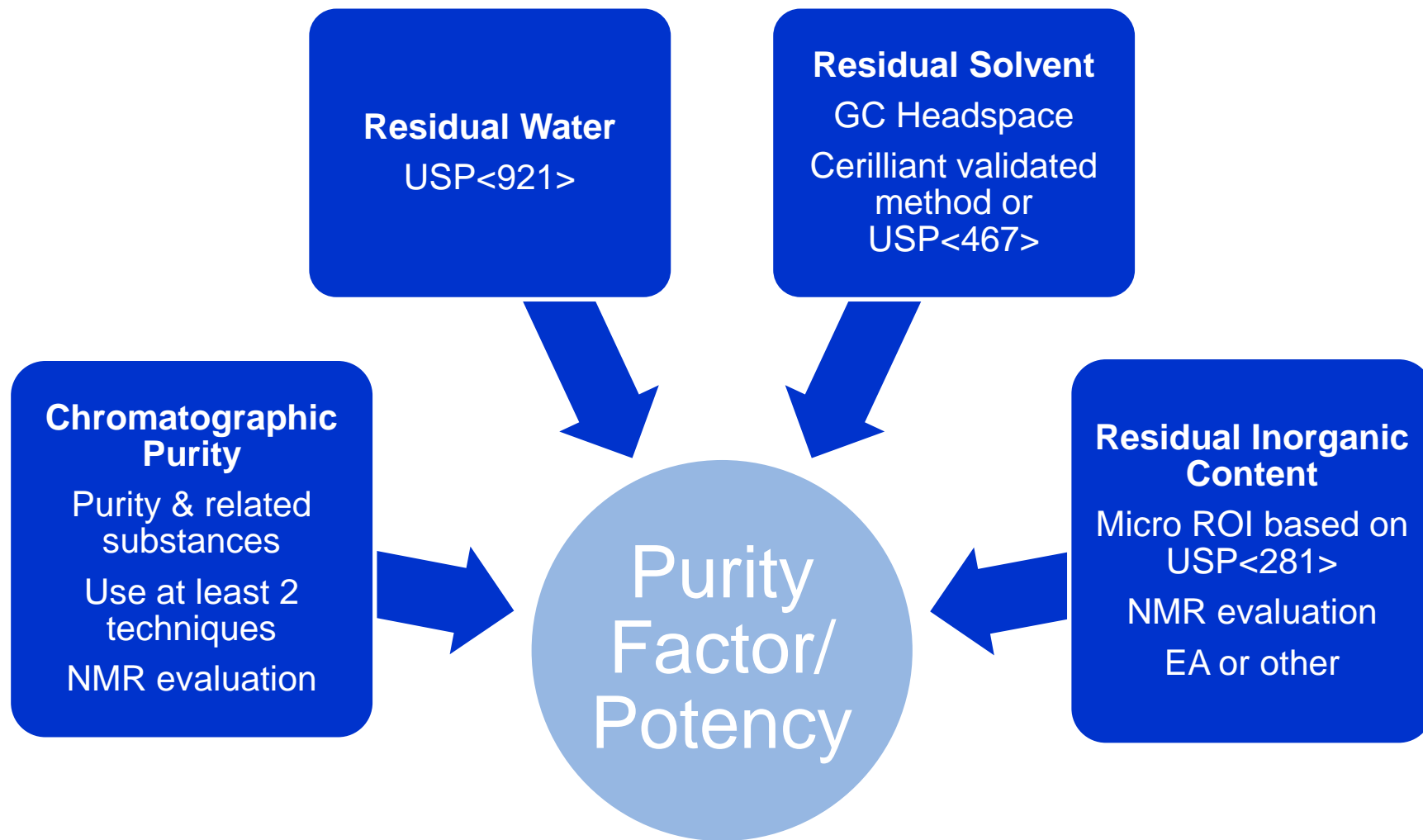
Identity

- Multiple techniques
 - 1D and 2D NMR
 - Proton
 - Carbon-13
 - Other nuclei
 - FTIR
 - GCMS, LCMS, LCMSMS
 - Other techniques as needed:
EA, Optical Rotation, DSC,
Melting Point, TGA
- Comparison to literature references

Purity / Potency

- Mass Balance – orthogonal approach
 - Multiple techniques for chrom purity and residuals
 - Based on ISO Guide 34
 - Used by NIST
 - Appropriate mass balance equation critical
- Assays – when appropriate
 - Availability of established methods with high precision
 - Availability of primary reference materials

Mass Balance – orthogonal approach



$$PurityFactor = \left[[100 - (wt\% Solvents) - (wt\% H_2O) - (wt\% Inorganics)] * \frac{ChromPurity}{100} \right]^{11}$$

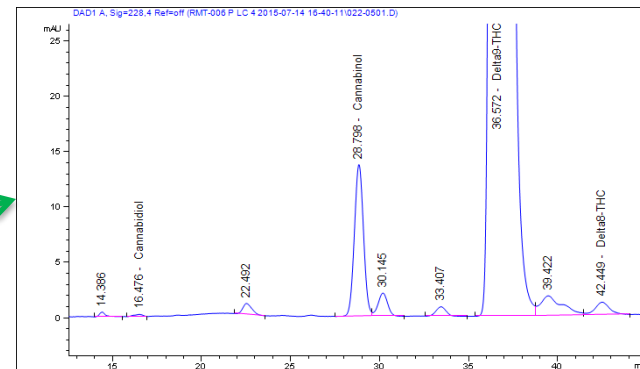
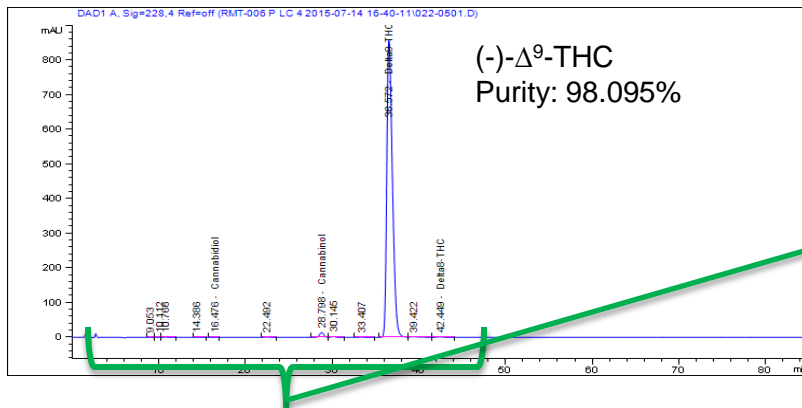
Analytical challenges with testing *Cannabis* cannabinoid biomarkers

Impurity profiles and presence of one analyte in another

- Purity profile will contain related cannabinoids as impurities
- Relative response factors (RRFs) for impurities may be unknown complicating purity value determination by HPLC/UV
- RRFs for some THC-related impurities are highly variable
- Cannabinoid impurities have different UV absorption characteristics based on their structure
 - HPLC/UV may not reflect the actual level of certain impurities
 - Cannabinoids with higher aromaticity /conjugation have higher UV response : HPLC area % \neq Impurity content
- Orthogonal purity techniques such as GC/FID and LC/MS should be employed, however
 - Cannabinoid instability may cause compound breakdown on GC/FID systems
 - MS response of analytes may not be equivalent

Measuring impurities/cannabinoid profile by HPLC/UV

- Cannabinol and Cannabidiol
 - By HPLC at a wavelength of 228 nm, Cannabinol has a 2.7 fold higher response than Cannabidiol
 - Cannabidiol raw material showed a 1% Cannabinol impurity, this value must be divided by the relative response factor of 2.7 to provide the accurate result of a ~0.37% Cannabinol impurity



| Analyte | RRT | RRF | Unadjusted Purity % | Adjusted Purity % |
|---------------------|------|------|---------------------|-------------------|
| Cannabidiol | 0.45 | 1.14 | 0.02 | 0.02 |
| Cannabinol | 0.78 | 2.77 | 1.24 | 0.45 |
| Δ ⁸ -THC | 1.14 | 0.94 | 0.17 | 0.17 |
| Δ ⁹ -THC | 1.00 | 1.00 | 97.32 | 98.09 |

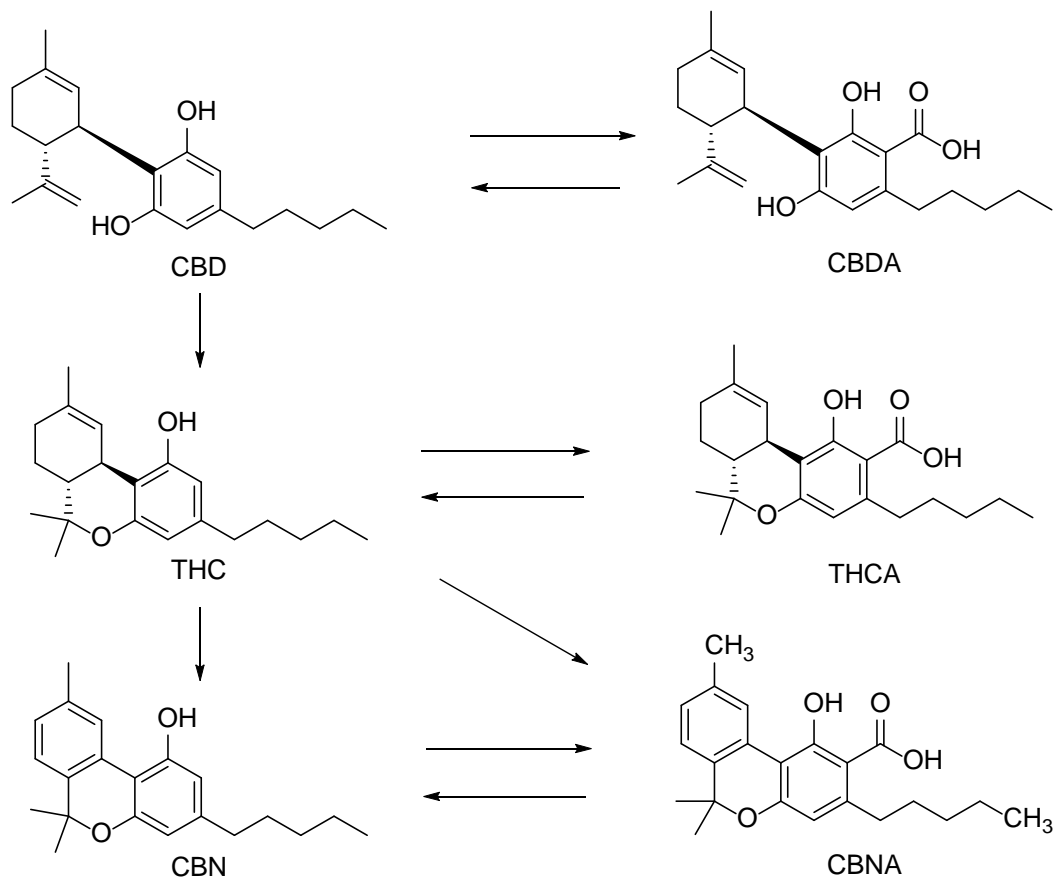
*Area% calculation, RRF between 0.9 and 1.1 will be considered as 1, this includes Cannabidiol and Δ⁸-THC

USP Tolerances

| Name | Relative Retention Time | Relative Response Factor | Limit (%) |
|---------------------------------------|-------------------------|--------------------------|-----------|
| Cannabinol | 0.78 | 2.7 | 1.5 |
| Δ ⁹ -Tetrahydrocannabinol | 1.00 | 1.0 | — |
| Exo-tetrahydrocannabinol ¹ | 1.07 | 0.92 | 0.5 |
| Δ ⁸ -Tetrahydrocannabinol | 1.18 | 0.90 | 2.0 |
| Any other individual impurity | — | 1.0 | 1.0 |

¹(6aR, 10aR)-6,6-Dimethyl-9-methylene-3-pentyl-6a,7,8,9,10,10a-hexahydro-6H-benzo[c]chromen-1-ol.

Impurity profiles – potential impurities

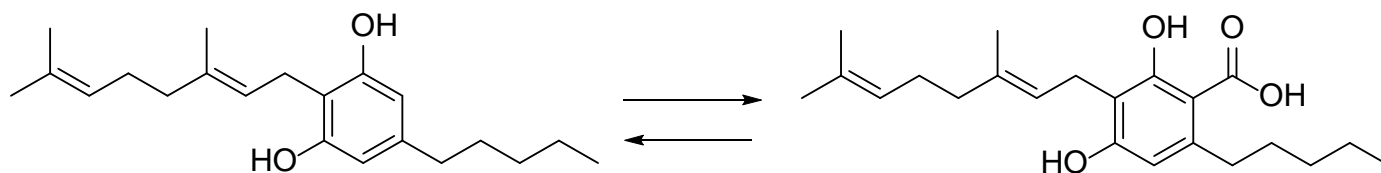


THCV analogs: Propyl side chain

- Related cannabinoids naturally occurring or due to oxidative degradation
- Derived from similar chemistries and can interconvert

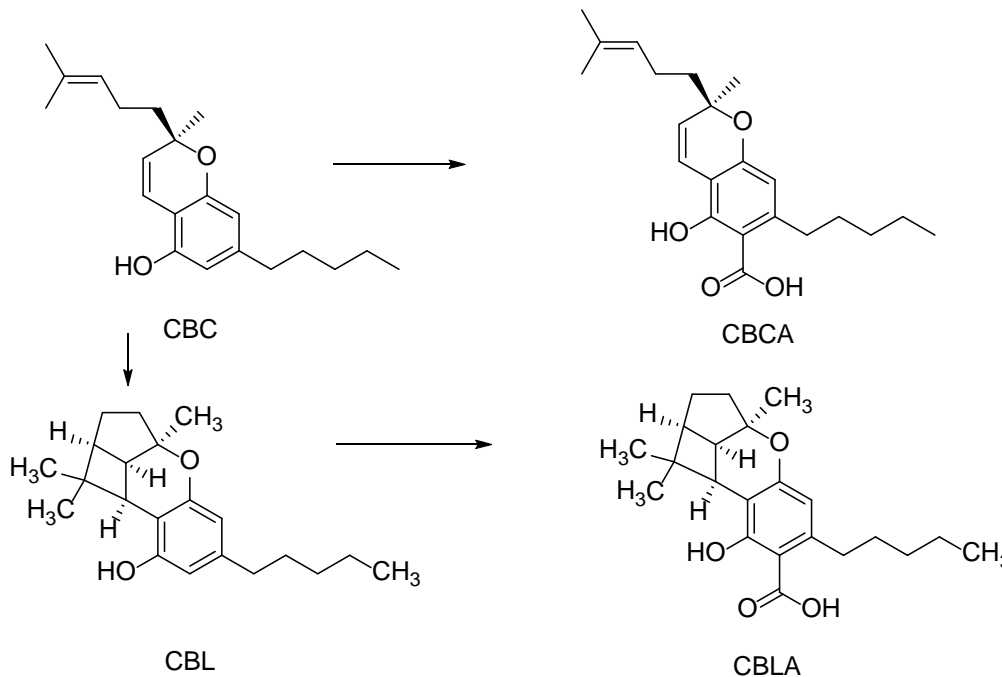
Impurity profiles – potential impurities

CBC & CBG Related Substances



CBG

Cannabigerolic acid CBGA



CBC

CBCA

CBL

CBLA

Complete characterization critical

Use of chromatographic purity alone can introduce error into the concentration of the reference solution; impurities in one CRM can contribute to an analyte of interest if not accounted for in mixes

| | Chrom. Purity (%) | Residual Solvent Content (%) | Residual Water Content (%) | Trace Inorganic Content (%) | Purity Factor for Quantitative Use (%) | PF Difference from Chrom Purity (%) | Catalog Number |
|--|-------------------|------------------------------|----------------------------|-----------------------------|--|-------------------------------------|----------------|
| Cannabidiol | 99.3 | 0.85 | Not detected | BQL | 98.43 | 0.90 | C-045 |
| Cannabinol | 99.5 | 3.39 | 0.11 | NA | 95.99 | 3.50 | C-046 |
| (-)- Δ^9 -THC | 98.6 | 1.47 | NA | NA | 98.70* | -0.10 | T-005 |
| Cannabigerol (CBG) | 99.0 | ND | BQL | BQL | 99.00 | 0.00 | C-141 |
| Cannabichromene (CBC) | 99.0 | ND | BQL | NA | 99.02 | 0.00 | C-143 |
| Cannabidiolic acid (CBDA) | 99.0 | 1.40 | BQL | BQL | 97.57 | 1.40 | C-144 |
| Cannabigerolic acid (CBGA) | 99.3 | 0.16 | ND | BQL | 99.11 | 0.20 | C-142 |
| Δ^9 -Tetrahydrocannabinolic acid A (THCA-A) | 98.4 | 0.41 | ND | BQL | 97.95 | 0.50 | T-093 |
| Tetrahydrocannabivarin (THCV) | 98.8 | 1.68 | BQL | NA | 97.18 | 1.60 | T-094 |
| Cannabidivarin (CBDV) | 98.8 | 0.91 | BQL | BQL | 97.90 | 0.90 | C-140 |

Impact is low due to documented specifications and robust manufacturing, testing and purification procedures.

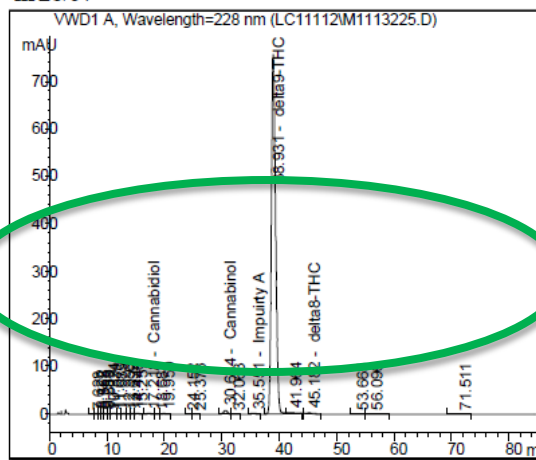
ND = None Detected; BQL = beyond quantitation limit (<0.2%)
*Chrom purity is adjusted and an average of two. Purity factor based on assay value

Example of impurity notation on COA

T-005
FE05271502
Revision 02
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Spectral and Physical Data

HPLC/UV



Column: Luna C18(2), 3.0 µm, 4.6 x 150 mm
Mobile Phase: Methanol::Water::Tetrahydrofuran (71::24::5)
Flow Rate: 1.0 mL/min
Wavelength: 228 nm
Data File Name: S:\HPLC\HPLC1\2012\LC11112M1113225.D
Instrument: LC#1
Sample Name: FC110112-02
Acquired: November 14, 2012

| Peak # | Ret Time | Area | Area % |
|--------|----------|----------|--------|
| 1 | 7.63 | 3.65 | 0.01 |
| 2 | 8.12 | 5.35 | 0.01 |
| 3 | 8.56 | 4.12 | 0.01 |
| 4 | 9.25 | 12.96 | 0.03 |
| 5 | 9.59 | 5.71 | 0.01 |
| 6 | 10.32 | 2.15 | 0.01 |
| 7 | 11.07 | 15.46 | 0.04 |
| 8 | 11.69 | 5.68 | 0.01 |
| 9 | 12.99 | 10.25 | 0.03 |
| 10 | 13.70 | 5.42 | 0.01 |
| 11 | 14.45 | 7.30 | 0.02 |
| 12 | 15.26 | 14.92 | 0.04 |
| 13 | 17.22 | 20.40 | 0.05 |
| 14 | 18.68 | 6.60 | 0.02 |
| 15 | 19.95 | 10.86 | 0.03 |
| 16 | 24.15 | 2.31 | 0.01 |
| 17 | 25.38 | 4.58 | 0.01 |
| 18 | 30.64 | 311.69 | 0.80 |
| 19 | 32.06 | 7.59 | 0.02 |
| 20 | 35.55 | 37.10 | 0.09 |
| 21 | 38.93 | 38449.20 | 98.25 |
| 22 | 41.96 | 72.52 | 0.19 |
| 23 | 45.18 | 87.42 | 0.22 |
| 24 | 53.67 | 12.35 | 0.03 |
| 25 | 56.10 | 11.08 | 0.03 |
| 26 | 71.51 | 7.84 | 0.02 |

Solution standard development

Goal is long term shelf life and suitability for intended use

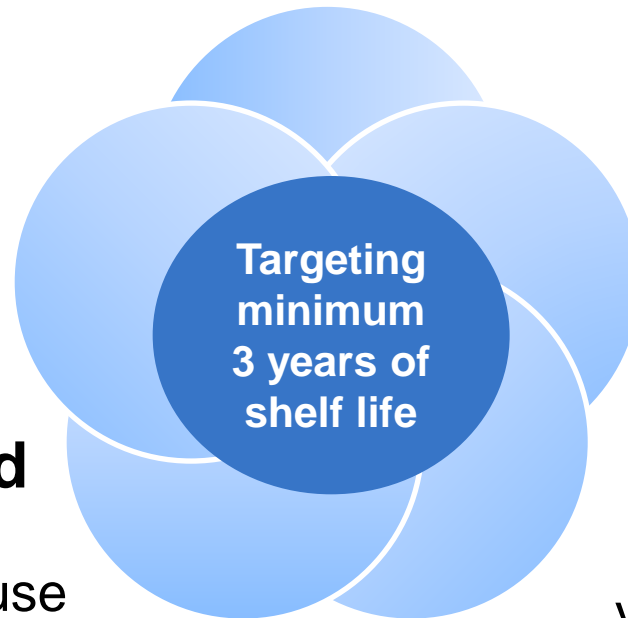
Understanding the Intended Use

Stability Studies

Accelerated at various
conditions
Precipitation
Degradation

Analytical Method Development

Interferences with end use
method
Resolution of known impurities



Material Properties

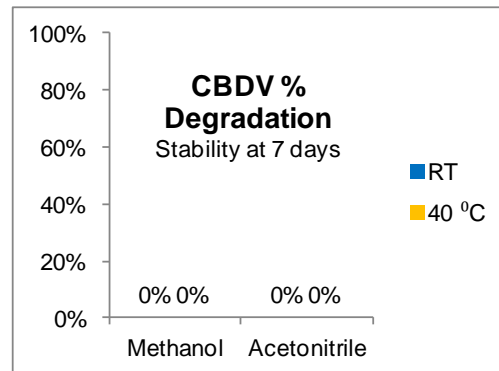
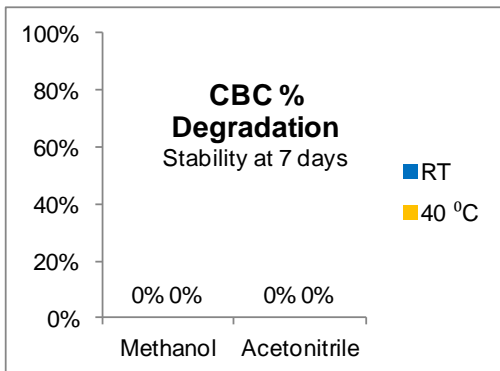
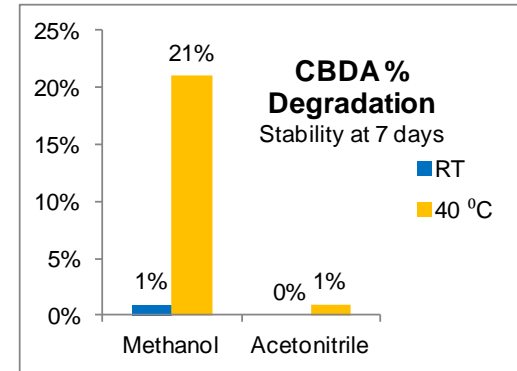
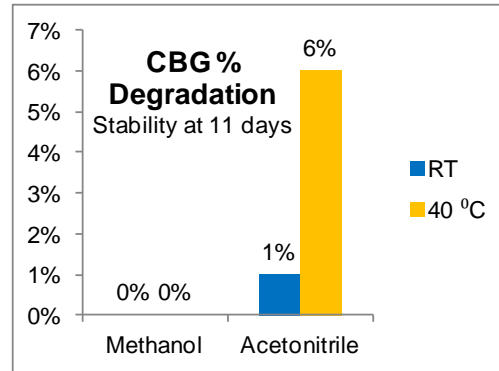
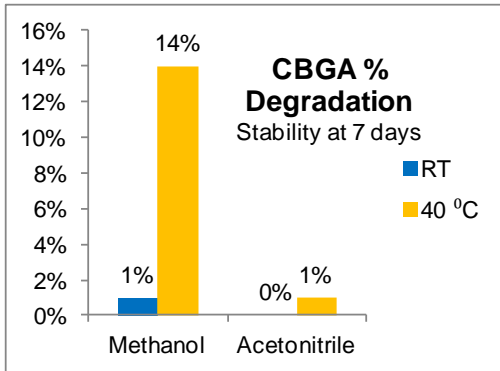
Handling & Preparation
Considerations
Hygroscopicity
Air & light sensitive
Potency / Toxicity

Diluent & Concentration

Solubility & Stability
Various solvents
Various concentrations
Suitability for end use

Solution development – challenges in selecting appropriate diluent

Methanol vs. Acetonitrile in accelerated studies



- Stability impacted by diluent and handling
- Stability controlled by validated processes, storage container, diluent quality, and inert gas overlay

Manufacturing

Robust manufacturing practices critical to accuracy & consistency

Material / Equipment Needs

- Hygroscopicity
- Sensitivity to air or light
- Static potential
- Viscosity / volatility
- Toxicity/potency
- Room selection
- Environmental controls – glove box

Gravimetric Preparation

- Weight/Weight
- Higher precision vs. volumetric
- Balance selection
- Batch size flexibility vs. volumetric
- Traceability with weigh tapes
- Repeatability

Dispensing

- Equipment checks
- Line purge
- Tubing & syringes
- Sampling plans
- Segregation
- Evaporation control

Handling challenges with *Cannabis* cannabinoid biomarkers

| | Physical form | O ₂ Sensitive | Heat Sensitive | Light |
|--|----------------|--------------------------|----------------|-------|
| Cannabidiol | Solid | ✓ | ✓ | |
| Cannabinol | Viscous liquid | ✓ | | |
| Cannabidivarin (CBDV) | Solid | ✓ | ✓ | |
| Cannabidiolic acid (CBDA) | Solid | ✓ | ✓ | |
| Cannabigerol (CBG) | Solid | ✓ | ✓ | |
| (-)- Δ^9 -THC | Glassy solid | ✓ | ✓ | ✓ |
| Cannabigerolic acid (CBGA) | Solid | | ✓ | |
| Tetrahydrocannabivarin (THCV) | Glassy solid | ✓ | ✓ | ✓ |
| Δ^9 -Tetrahydrocannabinolic acid A (THCA-A) | Foam | | ✓ | |
| Cannabichromene (CBC) | Viscous liquid | ✓ | ✓ | ✓ |

- Difficult to handle materials; some viscous liquids or “glassy” solids
- Glassy solids / liquids are hard to handle: sticky or so hard they cannot be weighed without melting
- Sensitive to air, light and heat – requiring glove box weighing in low actinic lighting
 - THC, THCV & CBC: Rapid darkening upon exposure to oxygen
 - Oxidative degradation produces a large number of polar impurities (eluting early under reverse-phase chromatography conditions)
 - THCV is not stable for more than an hour or two unless immediately put into a diluent

Certification of the solution standard

Certified gravimetric preparation supported by analytical verification of purity, concentration & homogeneity

Consistency

Lot-to-lot consistency verified by comparing to the previous lot

Homogeneity

Across the batch of ampoules/vials

Accuracy

Comparison to a primary source or certified second source – curve/calibration standard
Comparison of multiple independent preparations

Purity

Consistent with neat material
No contamination or degradation

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F99101501
Revision 00
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Cerilliant
ANALYTICAL REFERENCE STANDARDS

Certified Reference Material - Certificate of Analysis

(-)- Δ^9 -THC, Primary Standard

Certified Purity

ISO 61908 34
ISO 9001 1999
ISO 13485
ISO 15184
ISO 9001
GMV010P

Catalog Number: T-005
Lot: F99101501
Expiration: November 2020
Description: (-)- Δ^9 -THC in Methylene
Package: Solution in 2 mL amber USP Type I glass ampoule containing not less than 1 mL of certified solution.
Storage: Store unopened in freezer (-10 °C to 25 °C)
Shipping: Ambient - See Stability Section
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.

Instructions for Use: Users should quantitatively transfer desired volume using established good laboratory practices to apply this analyte or to dilute to the desired concentration. Each ampoule is intended for one-time use.
Regulatory: UN3251 Flammable (Liquid) TC 6.1-6.5 **Hazard:** Flammable, See Safety Data Sheet

- Expiration date has been established through real-time stability studies.
- Ampoules are overfilled to assure a minimum 1 mL volume can be transferred when using a 1 mL Class A volumetric pipette.
- For quantitative applications, the maximum sample size for standard use is 1 μ L.

| Analyte | Certified Concentration Value |
|----------------------|-------------------------------|
| (-)- Δ^9 -THC | 1.000 ± 0.004 mg/mL |

Method: GC-MS/MS
 • Concentration of the concentrate is prepared as an empirical standard in accordance with ISO 17025 and ISO 9001 and the appropriate 95% confidence interval using a primary source of (-)- Δ^9 -THC and has been subjected to statistical analysis of the production control and acceptance acceptance of the good laboratory practice standard methods, such as weighing balance.
 • This standard has been gravimetrically prepared using high-purity (-)- Δ^9 -THC and has been fully qualified and calibrated to the SI and higher order standards through an extensive chain of comparisons to realize the SI unit of mass.
 • This standard is prepared gravimetrically and mass results are reported as the conventional basis for weighing in SI. Nominal concentration is calculated based on the actual measured mass, Molar Volume, Purity Factor of the analytical, measured mass of the solution, and the density of the pure substance at 20 °C.
 • Concentration is certified for the concentration, purity, residual mass, residual volume and residual impurities. Uncertainty associated with mass, purity, and calibration information available upon request.

Metrological Traceability
 • This standard has been prepared and certified in accordance with the SI units, the SI and higher order standards through an extensive chain of comparisons to realize the SI unit of mass.
 • This standard has been gravimetrically prepared using high-purity (-)- Δ^9 -THC and has been fully qualified and calibrated to the SI and higher order standards through an extensive chain of comparisons to realize the SI unit of mass.
 • This standard is prepared gravimetrically and mass results are reported as the conventional basis for weighing in SI. Nominal concentration is calculated based on the actual measured mass, Molar Volume, Purity Factor of the analytical, measured mass of the solution, and the density of the pure substance at 20 °C.
 • Concentration is certified for the concentration, purity, residual mass, residual volume and residual impurities. Uncertainty associated with mass, purity, and calibration information available upon request.
 • ISO 9001 and gravimetrically certified through the weighing process using purified and calibrated balance.
 • Concentration is verified against an independently prepared calibration solution gravimetrically prepared.
 • Each lot is certified against the same standard and through the use of multiple analytical techniques. Analytical data is certified on subsequent pages of the COA. The density and molar volume of the standard is traceable to the SI and higher order standards through mass measurement and instrument qualification and calibration.

ANAB
Dillon Ellsworth, Quality Assurance Manager
December 09, 2015
Date

Cerilliant Corporation 811 Paloma Drive, Suite A, Round Rock, TX 78665 800.648.7837 / 512.238.9774

Assessment of solution stability

Ampouled format promotes stability by preventing evaporation & degradation due to presence of oxygen

- Accelerated stability– determination of requirements for transport and short term use at the bench
 - Qualified shippers and packing protocols
 - Shipping studies determine extremes encountered during transit
 - Accelerated data determines need for shipment under controlled conditions
 - Data supports short-term excursions and normal lab use
- Real-time stability collected upon release of new lots
- Concentration verification of solution standards compared to a calibration standard
- Initial assignment of retest date and tested per a protocol until shelf life is established

Stability – purity & concentration

Properly designed & prepared ampouled solutions can be stable for many years

| Compound | Solvent | Stability | Purity | | Analyzed Concentration | |
|--------------------|----------|---------------------------------|-----------------|--------------------|------------------------|--------------------|
| | | | Original | Stability Interval | Original | Stability Interval |
| Cannabinol | Methanol | 42 months Refrigerate | 99.7% at 228 nm | 99.3% at 228 nm | 0.991 mg/mL | 0.979 mg/mL |
| Cannabidiol | Methanol | 47 months Refrigerate | 99.7% at 228 nm | 99.6% at 228 nm | 1.002 mg/mL | 0.974 mg/mL |
| Cannabigerol (CBG) | Methanol | 12 months Freeze | 99.1% at 225 nm | 99.2% at 225 nm | 1.001 mg/mL | 0.997 mg/mL |

Concentration acceptance criteria for each of the examples = $\pm 3\%$ and incorporates variability of the analysis.

| LONG TERM STABILITY | | | |
|--|--------------|-------------|-----------|
| Compound | Solvent | Storage | Stability |
| Cannabidiol | Methanol | Freezer | 60 months |
| Cannabinol | Methanol | Freezer | 56 months |
| Cannabidivarin (CBDV) | Methanol | Sub-Freezer | 12 months |
| Cannabidiolic acid (CBDA) | Acetonitrile | Sub-Freezer | 8 months |
| Cannabigerol (CBG) | Methanol | Freezer | 12 months |
| (-)- Δ^9 -THC | Methanol | Freezer | 60 months |
| Cannabigerolic acid (CBGA) | Acetonitrile | Sub-Freezer | 11 months |
| Tetrahydrocannabivarin (THCV) | Methanol | Sub-Freezer | 3 months |
| Δ^9 -Tetrahydrocannabinolic acid A (THCA) | Acetonitrile | Sub-Freezer | 6 months |
| Cannabichromene (CBC) | Methanol | Freezer | 15 months |

Example stability section of a COA

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. | | |
| Short Term Storage: Stability data supports short term storage for up to 12 months at Refrigerate conditions. | | |
| Long Term Stability: Long term stability has been assessed for Freezer storage (-10 °C to -25 °C) conditions. Stability of a minimum of 60 months has been established through real-time stability studies. | | |

*Sub-freezer= -70 °C

Comprehensive COA

Includes full details of all analyses, including method, run conditions, chromatograms, and spectral data

- Expiration/retest date
- Isotopic purity
- Concentration & uncertainty
- Uncertainty statement
- Analytical verification of concentration
- Ampoule to ampoule consistency
- Traceability statement
- Solution standard assay
- Neat material characterization summary & purity factor assignment
 - Chromatographic purity
 - Residuals & method details
 - Purity factor
 - Identity
- Storage
- Stability data



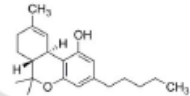
Cerilliant[®]
Analytical Reference Standards
A BONA-ALCOCHEM company

T-005
FE09101501
Revision 00
Page 1 of 7
Product of USA

Certified Reference Material - Certificate of Analysis

(-)- Δ^8 -THC, Primary Standard

Catalog Number: T-005
Lot: FE09101501
Expiration: November 2020
Description: (-)- Δ^8 -THC in Methanol.
Packaging: Solution in 2 mL amber USP Type I glass ampoule containing not less than 1 mL of certified solution.
Storage: Store unopened in freezer (-10 °C to -25 °C).
Shipping: Ambient. See Stability Section.
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.



Ce-Ref Quality

ISO 9000:04
ISO/IEC 17025
ISO 13485
ISO 15194
ISO 9001
GMP/GIP

Instructions for 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.

Regulatory: USDEA Exempt | Canadian TK # 61-65 **Safety:** **Danger.** See Safety Data Sheet.

- Expiration date has been established through real time stability studies.
- Ampoules are overfilled to ensure a minimum 1 mL volume can be transferred when using a 1 mL Class A volumetric pipette.
- For quantitative applications, the minimum sample size for intended use is 1 μ L.


| Analyte | Certified Concentration Value |
|----------------------|-------------------------------|
| (-)- Δ^8 -THC | 1.000 \pm 0.044 mg/mL |

- Uncertainty of the concentration is expressed as an expanded uncertainty in accordance with ISO 17025 and Guide M4 at the approximate 95% confidence interval using a coverage factor of $k = 2$ and has been calculated by statistical analysis of our production system and incorporates uncertainty of the mass balance purity factor, material density, balance, and weighing techniques.
- This standard is prepared gravimetrically and mass results are reported on the conventional basis for weighing in air. Nominal concentration is calculated based on the actual measured mass, Mass Balance Purity Factor of the analytical measured mass of the solution, and the density of the pure chemical at 20 °C.
- Concentration is corrected for chromatographic purity, residual water, residual solvents and residual inorganic. No adjustment required before use.
- Additional certification information available upon request.

Metrological Traceability

- This standard has been prepared and certified under the ISO Guide 34, ISO/IEC 17025, ISO 9001 and ISO 13485 standards. This standard meets the requirements of a Certified Reference Material and a Primary Standard as defined by ISO and is traceable to the SI and higher order standards through an unbroken chain of comparisons.
- 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 tolerance of $\pm 0.1\%$ relative error. Balance calibration adjustments are performed weekly utilizing the balance's internal adjustment mechanism. Calibration verifications are performed pre-use. Weigh tapes from the calibration verification are included in the production batch record for this standard. Production data package available upon request.
- 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.
- Each raw material utilized has been identified and thoroughly characterized through the use of multiple analytical techniques. Spectral data is provided on subsequent pages of the COA. The density and material Mass Balance Purity Factor is traceable to the SI and higher order reference standards through mass measurement and instrument qualification and calibration.

Cerilliant certifies that this standard meets the specifications stated in this certificate and warrants this product to meet the stated acceptance criteria through the expiration/retest date when stored unopened as recommended. Product should be used shortly after opening to avoid concentration changes due to evaporation. Warranty does not apply to ampoules stored after opening.



Daron Ellsworth, Quality Assurance Manager

[Signature]

December 09, 2015

Date

Cerilliant Corporation 811 Poloma Drive, Suite A, Round Rock, TX 78665 800-848-7837 / 512-238-9974

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What makes a good reference material?

- Fully characterized high purity neat materials and high purity diluents
 - Careful assignment of chromatographic purity by multiple methods
 - Analysis of residual impurities including water, inorganics and solvent
- Sound understanding of material characteristics through design & development
- Validated preparation process ensuring consistency and accuracy of solution concentration, purity & stability
- Qualified balances in their installed state with minimum weighings set for <math><0.1\%</math> relative error
- Gravimetric approach in solvent addition
- Traceability to SI units
- Uncertainty statement encompassing all aspects of standard preparation from neat material characterization to solution preparation.
- Prepared in a stable ampouled format
- Preparation and certification by an ISO Guide 34 and ISO 17025 accredited laboratory whose quality systems are also compliant to GMP and GLP

**Pre-made ampouled certified solution standards
A significant advantage over neat reference materials...**

