Noramco Cannabidiol FDA Presentation

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Noramco™
Leader in Controlled Substances

Noramco at a Glance

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Active ingredients for regulated cannabinoid therapies and APIs for other regulated applications

Company

More than 40 years experience and expertise

API sold in 30+ countries; 24 Active Type II US DMFs alone

Headquarters in Wilmington, Delaware with three facilities

Cannabinoids Experience

10+ years manufacturing THC in sesame oil (dronabinol DMF 20682)

Manufacture of cannabidiol (CBD) since 2016 (DMF 33223)

CBN, CBG, THC-V, CBD-V, and 30+ cannabinoids

Capabilities

Fully cGMP-compliant (FDA and DEA inspected and regulated)

Demonstrated total capacity of >750,000 kg annually in state-of-art facilities

Wilmington, Delaware
Manufacturing and Headquarters

Athens, Georgia
Global R&D and Manufacturing

Neuhausen, Switzerland
EMEA Commercial Hub (Not Shown)

Noramco Cannabidiol (CBD)

Manufacture detailed in **DMF 33223**

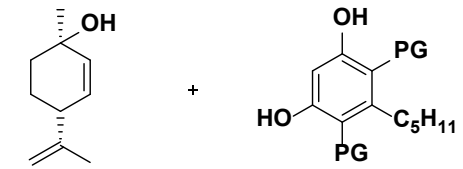
Large CBD capacity (>180,000Kg per annum)

cGMP assures quality, purity, consistency and stability

Continuity and **control of supply chain**

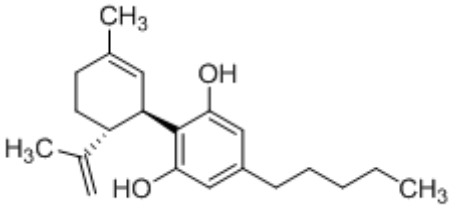
Globally recognized **regulatory compliance standards**

cGMP Regulatory Starting Materials



Menthadienol **Protected Olivetol**

High-purity Cannabidiol



Noramco manufactures synthetic CBD according to cGMP (ICH Q7 and applicable sections of 21 C.F.R. Parts 210 and 211)

Noramco utilizes validated analytical test methods and rigorous quality systems

Noramco monitors its CBD active ingredient for stability

Significant advantages to synthetic production:

- No heavy metals (e.g. lead) from soil
- No pesticide residues
- No environmental influences on quality such as rain, sunlight & soil nutrients
- No impurities from plant to remove

Formal FDA-administered cGMP procedures assure quality, purity, consistency and stability.

Mislabeled and Impure CBD Prevalent in Marketplace

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JAMA study finds 69% of 84 Cannabidiol Extract Products Mislabeled[1]

CBD in 84 products analyzed; **69% mislabeled**. Triggered FDA warning letters to 14 businesses in 2017

Average THC of 0.4% observed; enough to produce intoxication or impairment, especially among children.

52 people sickened in Utah by vaping 4-cyano-cumyl-butinaca (4-CCB) misrepresented as CBD[2]

2018 CDC report found that more than half of 52 possible cases either tested positive for non-cannabinoid synthetic compound called **4-cyano-cumyl-butinaca (4-CCB)** in product called Yolo CBD Oil. Efforts to determine company manufacturing Yolo CBD Oil unsuccessful.

Contaminated "cannabinoid" vaping liquid in Virginia contained 5-fluoro MDMB-PINACA (5F-ADB) misrepresented as CBD[3]

Vaping liquid in Virginia contained **5-fluoro MDMB-PINACA or 5F-ADB**, a DEA controlled substance known to trigger paranoia, panic attacks, increased heart rate and blood pressure, and cause convulsions, organ damage, and death. The analysis also found **dextromethorphan**.

These **selected** examples **highlight the need for federal oversight** of manufacturing, testing and distribution of CBD products.

[1] Labeling Accuracy of Cannabidiol Extracts Sold Online" Marcel O. Bonn-Miller, PhD[1]; Mallory J. E. Loflin, PhD[2]; Brian F. Thomas, PhD[3]; *et al, JAMA*. 2017;318(17):1708-1709. https://jamanetwork.com/journals/jama/fullarticle/2661569

[2] Horth RZ, Crouch B, Horowitz BZ, *et al. Notes from the Field:* Acute Poisonings from a Synthetic Cannabinoid Sold as Cannabidiol — Utah, 2017–2018. MMWR Morb Mortal Wkly Rep 2018;67:587–588. DOI: http://dx.doi.org/10.15585/mmwr.mm6720a5

[3] "The unexpected identification of the cannabimimetic, 5F-ADB, and dextromethorphan in commercially available cannabidiol e-liquids" J. Poklisa, H. Mulderb, M Peaceb , Forensic Science International, Volume 294, January 2019, Pages e25-e27 https://www.sciencedirect.com/science/article/pii/S0379073818307047?via%3Dihub

Comment 1: cGMP Production Essential to Provide Safe CBD

cGMPs exist for Food, Supplements and Drugs (21 CFR Parts 117, 111, 211, respectively)

Contain minimum requirements for methods, facilities and controls used in manufacturing, processing and packaging[1]

CBD from Noramco produced according to cGMP requirements (ICH Q7A and 21 C.F.R. Parts 210 and 211)

cGMP Key Attributes

Facilities	Processes + Testing	Quality Systems
Design	Appropriate Design	Operating Procedures
Monitoring	Qualified Personnel	Qualified Raw Materials
Operation	Suitable Equipment	Investigations

Assures identity, strength, quality and purity

Helps prevent instances of contamination, mix-ups, deviations, failures and errors

FDA-2019-N-1482 Comment

Compliance with 21 CFR Part 117, 111, 210 or 211 as appropriate should be **required** to demonstrate cGMP compliance for **human or animal** applications regardless of:

- **CBD origin** (extraction or synthesis)
- **Intended use** (drug, supplement or food)
- **Delivery** mechanism (oral, topical or inhalation)

[1] https://www.fda.gov/drugs/pharmaceutical-quality-resources/facts-about-current-good-manufacturing-practices-cgmps

Comment 2: Limit THC Impurity Level to 0.1% in CBD

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Factors supporting limit of 0.1% d9-THC:

1. Only FDA approved CBD containing drug (Epidiolex)[1] has reported limit of 0.1% THC
2. FDA 8-factor analysis evaluated CBD with less than 0.1% THC; determined does not meet criteria for scheduling under Single Convention[2]
3. ICH Q3A control of impurities would limit THC to 0.15% as ordinary identified but unqualified impurity
4. WHO ECDD Critical Review supported limit of 0.1% THC[3]
5. Noramco produces synthetic CBD at commercial scale; submitted Drug Master File (DMF 33223) committing to delta-9-tetrahydrocannabinol ("THC") limit ≤ 0.10 percent

   In practice, Noramco's THC levels less than 0.001 percent (10ppm)

FDA-2019-N-1482 Comment

CBD producers (extraction or synthetic) should control THC to ≤ 0.1% (Noramco has committed to ≤ 0.10% in DMF 33223)

[1] Epidiolex registered trademark of GW Pharmaceuticals, approved June 2018

[2] *FDA, Basis for the Recommendation to Place Cannabidiol in Schedule V of the CSA, 2 (May 16, 2018, Patterson Letter from HHS)*

[3] WHO, Cannabidiol (CBD) Critical Review Report, ECDD Fortieth Meeting, 17 (June 4-7, 2018)

Comment 3: Tightly Control Related Substances (Impurities)

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ICH guidelines[1] outline requirements from FDA and global regulators for allowable levels of related substances, setting specifications and for assessing stability

In 2019, Noramco purchased and analyzed five different publicly available CBD products represented as Active Ingredients.

Noramco analysis using certified analytical reference standards and scientifically sound analytical methods confirmed related substances of ***up to 4.39% (over 1,000 times higher)[2] than Noramco CBD.***

2019 Noramco Manufacturing Campaign 1 Results

Test	Specification	Lot 19154074	Lot 19194041	Lot 19144021	Lot 19154071	Lot 19124053
Description	White to slightly beige crystalline powder	Complies	Complies	Complies	Complies	Complies
Identification (IR)	Complies with reference	Complies	Complies	Complies	Complies	Complies
Identification (HPLC)	Conforms to reference	Complies	Complies	Complies	Complies	Complies
Assay (HPLC)	97.0 – 102.0%	100.0%	99.7%	99.8%	99.9%	100.3%
Impurities (HPLC)[3]	Starting material (RSM-Olivetol) NMT 0.15%	ND	ND	ND	ND	ND
	Intermediate (4-mb-CBD): NMT 0.15%	ND	ND	ND	ND	ND
	Delta-9-THC: NMT 0.10%	ND	ND	ND	ND	ND
	Each unspecified impurity: NMT 0.10%	ND	ND	ND	ND	ND
	Total impurities: NMT 1.0%	ND	ND	ND	ND	ND

FDA-2019-N-1482 Comment

CBD producers (whether extraction or synthesis) should follow, where applicable, ICH guidelines or food or supplement equivalent for control of related substances

[1] https://www.ich.org/products/guidelines/quality/article/quality-guidelines.html; Q3A to Q3D for Impurities, Q6A to Q6B for Specifications, Q1A – Q1F for Stability

[2] Total Impurity results were 1.16%, 0.73%, 0.56%, 4.39%, 0.61%. Validation report DS-VAL-000113097

[3] ND = Below the LOQ of 0.02% for THC in HPLC method. Validation report DS-VAL-000113097

Comment 4: Assess Stability of Active Ingredients in Products

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Product stability and label accuracy over time can only be assured if CBD produced and monitored according to long established regulations

Stability example: Noramco CBD Batch C13547 stored at 40ºC and 75% relative humidity

Test	Specification	0 months	1 month	2 month	3 month	5 month
Description	White to slightly beige crystalline powder	Off-white powder	Off-white powder	Off-white powder	Off-white powder	Off-white powder
Assay (HPLC)	97.0 – 102.0%	-	99.5%	100.2%	98.8%	99.9%
Impurities (HPLC)[1]	RSM-Olv: NMT 0.15%	-	ND	ND	ND	ND
	4-mb-CBD: NMT 0.15%	-	ND	ND	ND	ND
	Delta-9-THC: NMT 0.10%	-	ND	ND	ND	ND
	Each unspecified impurity: NMT 0.10%	-	RRT 1.929 0.05%	RRT 1.932 0.07%	RRT 1.983 0.03%	RRT 1.918 0.04%
	Total impurities: NMT 1.0%	-	0.05%	0.07%	<0.05%	<0.05%
Related Substances, low level (HPLC)						
	Δ9-Tetrahydrocannabinol: For Information	26 ppm	14 ppm	9 ppm	<4 ppm (ND)	6 ppm
	Δ8-Tetrahydrocannabinol: For Information	-	22 ppm	20 ppm	30 ppm	36 ppm

FDA-2019-N-1482 Comment

CBD producers (whether extracted or synthetic) should follow ICH guidelines for monitoring and testing of their product stability

[1] ND = Below the LOQ of 0.02% for THC in HPLC method. Validation report DS-VAL-000113097

Closing and Summary of Requests

Noramco is specifically requesting, to extent FDA deems it appropriate:

1. Production of CBD for Food, Supplements or Drugs be required to be produced in compliance with cGMP requirements (21 CFR Part 117, 111, 210 or 211 as appropriate) for human or animal applications, regardless of CBD origin (extraction or synthesis), intended use (food, supplement, or drug), and irrespective of delivery mechanism (oral, topical or inhalation)
2. CBD producers (extraction or synthesis) should control THC to ≤ 0.1% (Noramco committed to 0.10% in DMF 33223)
3. FDA adopt ICH guidelines for control of related substances, setting specifications and for monitoring product stability for CBD producers (extraction or synthesis)
4. FDA work with United States Pharmacopeia (USP) to formulate manufacturing standards for pharmaceutical grade and dietary supplement grade CBD ingredients

Note: Noramco not suggesting that all CBD produced or consumed should be subject to full drug regulations

Summary:

Regardless of method of production or intended use for drugs, foods or supplements, ***patients and consumers deserve*** CBD produced in accordance with cGMP that is tested to assure identity, purity, quality and strength.

Noramco has demonstrated multi-ton compliant production is viable.