Standard Methods for Quality Assurance of Hemp Derived Natural Products

Holly E. Johnson, Ph.D.
Chief Science Officer
American Herbal Products Association
hjohnson@ahpa.org
Cannabis was included in the United States Pharmacopoeia for 92 years, 1850-1942.
Challenges in Quality Assurance of Cannabis & Hemp under US Regulations

• Complex biological matrix; homogeneity & sampling
• Lack of standard test methods & proficiency testing
• Reference materials
• Myriad finished products
• Food, drug, supplement??
• Lengthy prohibition...

Technical & Regulatory uncertainty
Standards

Standards setting organizations are working on standards specific to cannabis and hemp:
AHPA GACP-GMP

- Section 1 Definitions
- Section 2 Botanical identity and quality
- Section 3 thru 7 GACPs
- Section 8 Further processing and handling
- Section 9 Basic food facility GMPs
- Section 10 Recommendations for dietary ingredient suppliers
- Appendices of supporting information
AHPA GACP-GMP

• Section 1 Definitions
• Section 2 Botanical identity and quality
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GOOD AGRICULTURAL AND COLLECTION PRACTICES AND GOOD MANUFACTURING PRACTICES FOR BOTANICAL MATERIALS

CONTAINS NONBINDING RECOMMENDATIONS

March 2017
Prepared by the American Herbal Products Association

American Herbal Products Association
Cannabis oversight recommendations for regulators

Oversight framework promotes best practices for cannabis production and distribution from seed to consumption

AHPA developed the following recommendations to address four operational stages of cannabis production and distribution:

1. **Cultivation and processing operations** addresses cultivation practices, facility requirements, management of water resources, record keeping, and information disclosure. It also establishes best practices for operations that provide post-harvest processing of cannabis, for distribution to dispensing operations, or to manufacturing operations for the production of cannabis-derived products.

2. **Manufacturing and related operations** is generally modeled after federal current good manufacturing practice operational settings.

3. **Laboratory operations** is a complement to existing good laboratory practices; these recommendations focus on the personnel, security, sample handling and disposal, and data management and reporting activities that may be unique to laboratories analyzing cannabis samples.

4. **Dispensing operations** focuses on personnel, security, product acquisition, record keeping, customer policies, and other matters that can contribute to best practice in the dispensary setting.

Coming Soon: Hemp specific guidance
Standards

Standards setting organizations are working on standards specific to cannabis and hemp:

- American Herbal Pharmacopoeia
- USP (United States Pharmacopeia)
- AOAC INTERNATIONAL
- BSCG (Better Standards Certified Growers)
- US Hemp Authority
- ASTM INTERNATIONAL
- NSF
- AHPA (American Herbal Products Association)
- CASP (Cannabis Analytical Science Program)

Cannabis-Related AOAC Standard Method Performance Requirements:

- SMPR 2017.001 Cannabinoids in Cannabis Concentrates
- SMPR 2017.002 Cannabinoids in Dried Plant Materials
- SMPR 2017.019 Cannabinoids in Chocolate
- SMPR 2018.011 Pesticides in Cannabis
• **Subpart E 111.70** requires establishment of specifications for identity, purity, strength & composition:

• Sec. 111.70 What specifications must you establish?

• (b) For each **component** that you use in the manufacture of a dietary supplement, you must establish component specifications as follows:

• (1) You must establish an **identity** specification;

• (2) You must establish component specifications that are necessary to ensure that specifications for the **purity, strength and composition** of dietary supplements manufactured using the components are met; and

• (3) You must establish **limits on those types of contamination that may adulterate** or may lead to adulteration of the finished batch of the dietary supplement to ensure the quality of the dietary supplement.

In hemp, THC may be considered a contaminant that may adulterate – limit is NMT 0.3%
Setting Appropriate Specifications

Guidance for setting limits: heavy metals, microbiology, pesticides, solvents

AHPA: [www.ahpa.org](http://www.ahpa.org)

USP, WHO, FDA, NSF/ANSI, ...

AHP:
Subpart E 111.75 What must you do to determine whether specifications are met?

(a) Before you use a component, you must:

(1)(i) Conduct at least one appropriate test or examination ...... 

(h)(1) You must ensure that the tests and examinations that you use to determine whether the specifications are met are appropriate, scientifically valid methods.

(2) The tests and examinations that you use must include at least one of the following:

(i) Gross organoleptic analysis;

(ii) Macroscopic analysis;

(iii) Microscopic analysis;

(iv) Chemical analysis; or

(v) Other scientifically valid methods.

Establish corrective action plans for use when an established specification is not met.
Standard Analytical Methods

Standards setting organizations – Official methods for common materials
Selecting Scientifically Valid Methods

Standards setting organizations are working on standard methods specific to cannabis and hemp:

1. AOAC Official Methods of Action for cannabinoids in cannabis flower & extracts
Repeatability ($\text{RSD}_r$) and **Intermediate Precision** ($\text{RSD}_{i}$) for Cannabinoids in a Dried Plant Material

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Analyst 1</th>
<th>Analyst 2</th>
<th>Analyst 1 &amp; 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean conc. ($%$, w/w)</td>
<td>$\text{RSD}_r$ (n=5)</td>
<td>Mean conc. ($%$, w/w)</td>
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<tr>
<td>CBDVA</td>
<td>0.0389</td>
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<td>0.0355</td>
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<tr>
<td>CBDV</td>
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<td>0.0508</td>
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<tr>
<td>CBDA</td>
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<td>1.6</td>
<td>3.78</td>
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<tr>
<td>CBGA</td>
<td>0.257</td>
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<tr>
<td>CBG</td>
<td>0.0390</td>
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<tr>
<td>CBD</td>
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<td>4.2</td>
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<tr>
<td>$\Delta^9$-THC</td>
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<tr>
<td>THCA</td>
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<td>0.0856</td>
</tr>
<tr>
<td>CBC</td>
<td>0.0347</td>
<td>2.0</td>
<td>0.0343</td>
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</table>

Data: Courtesy of K. Mastovska, Eurofins Food Integrity & Innovation (Method AOAC First Action Official status)
Subpart J 111.320 What requirements apply to laboratory methods for testing and examination?

(a) You must verify that the laboratory examination and testing methodologies are appropriate for their intended use.

(b) You must identify and use an appropriate scientifically valid method for each established specification for which testing or examination is required to determine whether the specification is met.

Standard methods are scientifically valid for common materials, but must verify & document for complex finished products – scope matters.
21 CFR part 111

- Subpart J 111.320(a) requires verification that the laboratory test methods are appropriate for their intended use.

This method was developed and validated in accordance with current ICH and FDA guidance. Here is a summary of some the validation results:

- Linearity determined by seven point calibration curve: correlation coefficient (R2)>0.999
- Lower limit of detection: CBD = 0.072 µg/ml, THC = 0.088 µg/ml
- Lower limit of quantitation: CBD = 0.22 µg/ml, THC = 0.27 µg/ml
- Precision by repeatability and intermediate precision: % RSD for peak area <2%
- Specificity ensured with single quad mass spec and spectral purity by photodiode array.
- Accuracy verified with triplicate spikes at three levels in various matrices for both CBD & THC: recovery range = 97-103%
Scientifically Valid Methods – Specificity, Precision, Accuracy

- Methods must be fit for their intended use – scope matters!!
- USP method for Green tea extract & AOAC method for resveratrol
- Matrix extension & validation/verification for complex FP
Accurate, precise, specific methods for each matrix!
Standards setting organizations – Official methods for common materials – 2 OMAs for *Cannabis* inflorescence

3 CASP working groups:
- Microbiological contaminants
- Chemical contaminants
- Cannabinoids in hemp & consumables
Standards setting organizations – Official methods for common materials – 2 OMAs for *Cannabis* inflorescence

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Matrix</th>
<th>Deliverables</th>
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<tr>
<td>Cannabinoids</td>
<td>Hemp plant material</td>
<td>OMA</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>Hemp extracts</td>
<td>OMA</td>
</tr>
</tbody>
</table>
| Cannabinoids | Foods/beverages   | Sample prep method  
Guidance on matrix extension |
Standard methods are scientifically valid for common materials, but must verify & document for complex finished products – scope matters.
Chloroform was considered a “valuable ingredient” in this preparation, but would now be a residual solvent contaminant.
Thank You!

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