Topic	USP-ASTM Cannabis Quality – Potential Actions or Approaches
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Attention	Nandu Sarma and David Vaillencourt Re: USP and ASTM and workshop speakers and networks
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Cannabis Quality – the need for science-based global harmonisation of standards

Findings from the USP-ASTM Global Workshops on Cannabis Quality

Background

This summary of recent USP-ASTM workshops assessing cannabis quality offers a road map to inform greater alignment among governments, policymakers, regulators, standards organizations, industry, and laboratories and facilitate a more harmonized future related to cannabis quality standards.

Cannabis [*Cannabis sativa* L., Fam. Cannabaceae] and derived materials and products are increasingly available on a global level for medical and scientific use. The rapid expansion of the cannabis industry has led to misunderstandings and misinterpretations of the provisions that regulate cultivation, manufacture and distribution. [1] [2] Indeed, domestic regulations vary widely between states, territories, and countries across the globe.

To overcome the variability in regulatory practices, the global alignment of regulations, standards and practices is necessary. Alignment will allow regulators, standards organizations, industry, and laboratories to collectively ensure the safe supply of quality cannabis-derived materials and medical products.

> "The quality issue is a good starting point to find general agreement.
>
> From a scientific point of view, the more we have alignment of standards and practices, the better we have preconditions for global exchange."
>
> **Werner Knoess**, *Federal Institute for Drugs and Medical Devices (BfArM), Germany.*

To explore opportunities for harmonization around cannabis quality standards and to identify gaps in scientific knowledge, the United States Pharmacopeia (USP) and the American Society for Testing and Materials (ASTM) organized two online interactive public events with speakers representing regulatory agencies, standard setting organizations, industry, testing labs, the scientific community and policy makers. Detailed notes including the presentation materials are available at:

- **Part 1: ASTM International & USP Global Workshop on Cannabis Quality**
- **Part 2: Medical Cannabis Product Quality Webinar**

The USP-ASTM Cannabis Quality workshops explored the potential for harmonisation among regulators, standards organizations, analytical laboratories, and industry. Drawing on expert insights from the European

[1] The International Drug Control Treaties present multiple obligations of signatory governments: to ensure the availability and promote the rational use of narcotic drugs and psychotropic substances for medical and scientific purposes, and, to prevent their diversion and abuse. In particular, refer to The Single Convention on Narcotic Drugs, 1961 and The Convention on Psychotropic Substances, 1971.

[2] Consistent with the rational use of medicines (WHO 2020), eligible patients are those patients that meet the criteria for prescribing and where a cannabis-based medicine is a suitable choice and is appropriate to a patient's needs.

Union (EU), North America, sub-Saharan Africa, Southeast Asia and Oceania ensures these agreed-upon potential actions or approaches are rooted in current evidence and promote best practice.

The Cannabis Quality workshop objectives:

- Raise awareness of the existing global regulatory frameworks, quality standards, quality attributes, and best practices applied to cannabis for medical and scientific use.
- Increase understanding of the scientific basis for regulations, standards and practices, identify data gaps, and inform future research needs.
- Highlight common challenges faced by regulators, standards organizations, laboratories and industry.
- Foster global engagement and opportunities for information sharing and identification of key limitations, resources availability, and major action points for innovation required across the globe.

Potential Actions or Approaches

The following table is a summary of workshop findings, which is detailed in Appendix 2.

Table: Theme 1 - Regulatory Practices

The growth of the cannabis medicines industry and the globalisation of trade mean substances, materials and medical end products are produced and distributed in complex, fragmented supply chains that cross borders. Regulators must rely on other regulators who use different systems.
In a step toward consensus and a global standard, several jurisdictions have adopted a common set of definitions, a monograph or minimum quality standards, incorporated pharmacopeial methods, and the requirements of globally recognized good practices for manufacture.

Topic	Issue	Potential Action or Approach
Good regulatory practice	National authorities can improve communications to share best practices and promote common approaches to import and export.	Defining and licensing activities, certifications, good practices, and quality standards would reduce global variability. The adoption of uniform definitions is desirable, including specifications for chemotypes / defining categories of *Cannabis sativa* L.
Domestic regulations related to cannabis quality	Domestic regulations provide a platform for government institutions, industry, and the health profession to define and manage the risk associated with materials and products containing controlled drugs.	Consistency is needed for industry to operate effectively and efficiently. Opportunities for greater consistency include requirements for labelling, terpene content testing, microbial testing, water determination, batch sampling and sample preparation requirements, assay accuracy and the validation of test methods, and permissible contaminant limits, especially for pesticides.
Pesticide contamination	Testing for pesticides is required for cannabis. Hundreds of available and commercially used pesticides are used across the globe.	A global data source for pesticide identification could help assess the risk of contamination and the risk posed by contaminants. See table Theme 4.
Assay limits for dried cannabis flower	Cannabis is a botanical substance with multiple compounds that are difficult to standardise.	Globally, the assay for cannabinoids is linked to a batch release criteria which ranges from a ± 10 % to ± 20 % deviation. Scientific consensus would be required to determine whether ± 10 % or ± 20 % should apply to a medical product or to the herbal substance itself.
Laboratories	Dozens of regulatory frameworks exist and laboratories use different testing methods.	The adoption of pharmacopeial or consensus standards is recommended for laboratories, globally. See table theme 3 and 4.

		Regulators who adopt consensus standards and good practices reduce obstacles to effective regulatory control, the audit process, the collection and reporting of data, enforcing licenced activities, and the regulatory support required of industry. This includes assisting laboratories to validate methods and arbitrate lab-to-lab differences.

Table: Theme 2 - Standards and Good Practices

Standards organizations like USP and ASTM develop standards, guidelines and practices to help address pressing issues such as quality specifications, packaging and labeling standards, operational best practices and more.

Adopting published standards that set specifications for identity, cannabinoid content, limits for contaminants, and other quality attributes is fundamental to addressing common challenges and improve and create consistency in product quality across the globe.

Topic	Issue	Potential Action or Approach
Standardization in the cannabis industry	Non-standardized approaches by industry creates barriers for industry development and regulatory oversight.	Standardisation in cultivation and manufacture would help ensure consistent batch-to-batch cannabinoid content (w/w). This would help manufacturers manage input needs and industrial contracts, including supporting supplier verification and audit processes, and enable rules-based global trade.
Standards for the cannabis industry	Global alignment of standards and specifications for identity, cannabinoid content, limits for contaminants, and other quality attributes, and traceability of the starting materials through to the finished products do not currently exist. Standards would address the challenges of un-validated test methods, inaccurate label claims for cannabinoid content, varying limits for microbial and chemical contamination, and emerging concerns related to synthetic minor cannabinoids and impurities.	Establish clear lines of communication when developing cannabis quality standards to prevent duplication or misuse of limited resources.
Good practices for the cannabis industry	A good practice implies that strategies, approaches and activities undertaken have been shown through research and evaluation to be effective, efficient, sustainable and transferable, and to reliably lead to a desired result. Good Agricultural and Collection Practice (GACP) for medicinal use of cannabis is the only globe accepted set of requirements available to industry for the cultivation of cannabis. GACP alone is insufficient for cannabis flower intended for medical use by inhalation.	A new cultivation standard is needed for *Cannabis sativa* L. when intended for medical use and administration is by inhalation.

Table: Theme 3 - Monographs and methods

Harmonisation of testing methods and cross-laboratory validation is critical. Methods should be reliable, reproducible, and able to be up taken by industry. Issues raised during the workshops include unvalidated test methodologies, inaccurate label claims for cannabinoid content, varying limits for microbial load, pesticide residues, and heavy metal contamination. Other emerging issues, such as the concerns related to synthetically derived cannabinoids including Δ-8-THC and its impurities, were also discussed.

Topic	Issue	Potential Action or Approach
Primary focus on inflorescence of *Cannabis sativa* L.	Given the inflorescence of *Cannabis sativa* L. is the foundation of the industry and cannabis-derived medicines, it makes sense that harmonisation starts here.	A globally adopted cannabis inflorescence monograph would cover at a minimum: identification, assay for cannabinoid content, moisture content, and contaminants (foreign matter, microbial, heavy metal, and pesticide content).
Compliance-oriented monograph	There is inconsistency in quality requirements for Cannabis *sativa* L. across the globe.	A globally accepted compliance-oriented monograph for cannabis would decrease risk at the government and industry level, while aiming to eliminate methods which may increase variation. A monograph must consider the factors of cost (affordability), value (fit-for-purpose: practical, applicable and reliable), and adoption (accepted and used by industry and regulators around the globe).
Technical capacity of national authorities	The general technical capacity of 'Competent National Authorities' to measure the quality and quantity of controlled drugs is essential. Some nations may lack resources to effectively implement a laboratory control and testing programme. At the national level, in many countries, chemical analysis to low thresholds may not be possible given a lack of appropriate, cost-effective identification techniques, and because of available resources to achieve this long-term.	If resource availability and technical competencies at a national level are not available, reliance on industry Good Practices, Certificates of Analysis released by certified laboratories, Mutual Recognition Agreements, and a global cooperation on sharing knowledge is required.

Table: Theme 4 - Analytical / Laboratory

Analytical inconsistencies around the globe mean the industry and regulatory authorities are currently challenged by: (i) variability in laboratory practices, (ii) different analytical techniques and methodologies, (iii) inconstant quality of reference materials and standards.

Topic	Issue	Potential Action or Approach
Qualitative and quantitative analysis	Many more laboratories across the globe are now required to both qualitatively and quantitatively identify cannabis, derived material and products. Effective and well-resourced regulatory authorities are needed to audit laboratories and provide oversight for industries and markets.	Reduce variances in jurisdictional requirements for analysis, sample selection and preparation methods, sample homogeneity, and inconsistencies in pesticide and microbial contaminants testing.
Certifications and audit	Industry needs to have contractual quality agreements that specify the quality standards that must be applied to testing. This requires laboratories to take part in supplier qualification programmes and audits.	A minimum requirement for laboratory licensing, certification, and quality-assurance audits is required – for example as per GMP and ISO 17025.
Validation	Variation in instruments and by laboratory personnel will introduce a small amount of variability, which is amplified with lab-to-lab	Accredited laboratories are required to undertake cross-laboratory validation to confirm that comparable data is generated across

	differences. Eliminating intra- and inter-laboratory variation is a priority, given this issue currently confronts both industry and regulators.	multiple laboratories using the same methods. Participation in external proficiency testing programmes would align with GMP certification and ISO 17025 accreditation requirements.
Sampling and sample preparation	Batch sample selection and sample preparation methodology is critical. Harmonisation of sampling protocols, their submission to laboratories, and the sample preparation procedures for testing is needed.	Sampling should consider the distribution of the compounds across the cannabis plant and herbal material representing the batch. Strict protocols are needed, as the quality of the sample is additionally affected by the production environment.
LoD vs aW	The moisture / water content of cannabis inflorescence can result in microbial growth, affecting the quality and safety of the material. Two methods for determining moisture / water content of cannabis inflorescence are Loss on Drying (LoD) and Water Activity (aW). aW has not been widely used in the medico-scientific industry for cannabis materials. LoD is widely used to determine the moisture content and to calculate the cannabinoid content on a weight for weight basis (e.g., % THC w/w). Additionally, this quantitative data is used for industrial contracts and licensing.	The most suitable method is still requires further investigation. In the meantime, analysis of a standardised reference cannabis material, over numerous batches, is needed to determine the comparability of the two methods.
Contaminants	Pesticides are a major contamination risk. There are hundreds of commercially used pesticides, and the risk of contamination differs between indoor (controlled) and outdoor (uncontrolled) growing environments. When cultivating outdoors, there are challenges around pesticides, as well as microbial, heavy metal and residual solvent contamination. These contaminants can be differ in their concentration throughout the collected sample.	It is necessary to better understand the production processes and inherent risks of contamination for each cannabis product. A global data source for pesticides and a pesticide testing framework is needed. The best framework is still to be determined through scientific discourse – a risk-based matrix, a screening matrix, or a hybrid approach.
Certificates of Analysis	Industry and regulatory authorities around the world are challenged by analytical inconsistencies (e.g., irregular lab practices, inconsistent analytical methods, variable quality reference materials and in the samples and sample preparations). The variability in analytical laboratories presents challenges for the validity of Certificates of Analysis (CoAs). In some circumstances it can be difficult to determine if the CoA accurately reflects the quality of the material or product it represents.	A uniform CoA, issued by validated laboratories for batch identification, traceability and quality is required to overcome this situation. The CoA would correspond to information on the label of the material and medicine. This CoA, at a minimum, would contain information about the cannabinoids present, characteristics of the makeup of the product, and quantify the contents and prove the consistency of the product.
Essentials of identification and analysis	Technical questions on quality control, identification and analysis need to be explored further. Pressing questions include: **Analytical procedures** What are the best and most effective fit for purpose analytical procedures for establishing the identity of different chemotypes? **Reference substances**	Additional investigation is required to address these questions.

	What are appropriate reference substances for quantitative and qualitative use? **Assay** What is the suitability test acceptance criteria, based on the chromatographic separation of acidic and neutral cannabinoids? **Foreign matter** What is the definition of foreign matter in herbal substances (i.e.., cannabis flower) and herbal products? **Stability** What stability tests are undertaken for the herbal substance and the herbal product, including defining storage conditions, intermediate conditions, long-term stability, and photo stability testing requirements?	

Appendix 1: Overview of the Cannabis Quality workshops

The USP and ASTM hosted regulators, scientists, industry, and policy makers at two online interactive public events:

- **Part 1: ASTM International & USP Global Workshop on Cannabis Quality**
- **Part 2: Medical Cannabis Product Quality Webinar**

Part one: Europe and North America

In December 2022, ASTM International and USP co-sponsored a workshop on cannabis quality with inputs from regulators, standards organizations, industry, and analytical laboratories from the Americas and Europe.

More than 500 global delegates discussed regulatory and industry challenges related to cannabis quality and a science-based approach to the harmonization of cannabis quality requirements.

Workshop Objectives:

- Increase awareness of the existing data, regulatory frameworks and guidance, quality standards and quality attributes surrounding cannabis for medical and scientific use – initially from an American and European perspective.
- Understand the scientific basis for standards and practices related to cannabis quality.
- Identify needs, challenges and data gaps related to cannabis quality to inform future standards, practices and research needs.

Workshop two: sub-Saharan Africa, Oceania, and Southeast Asia

In June 2023, to broaden the conversation, and to confirm the findings from the first workshop, experts in sub-Saharan Africa, Southeast Asia and Oceania attended the second online workshop. This ensured a truly global and collaborative approach to addressing the challenges and opportunities to work towards alignment.

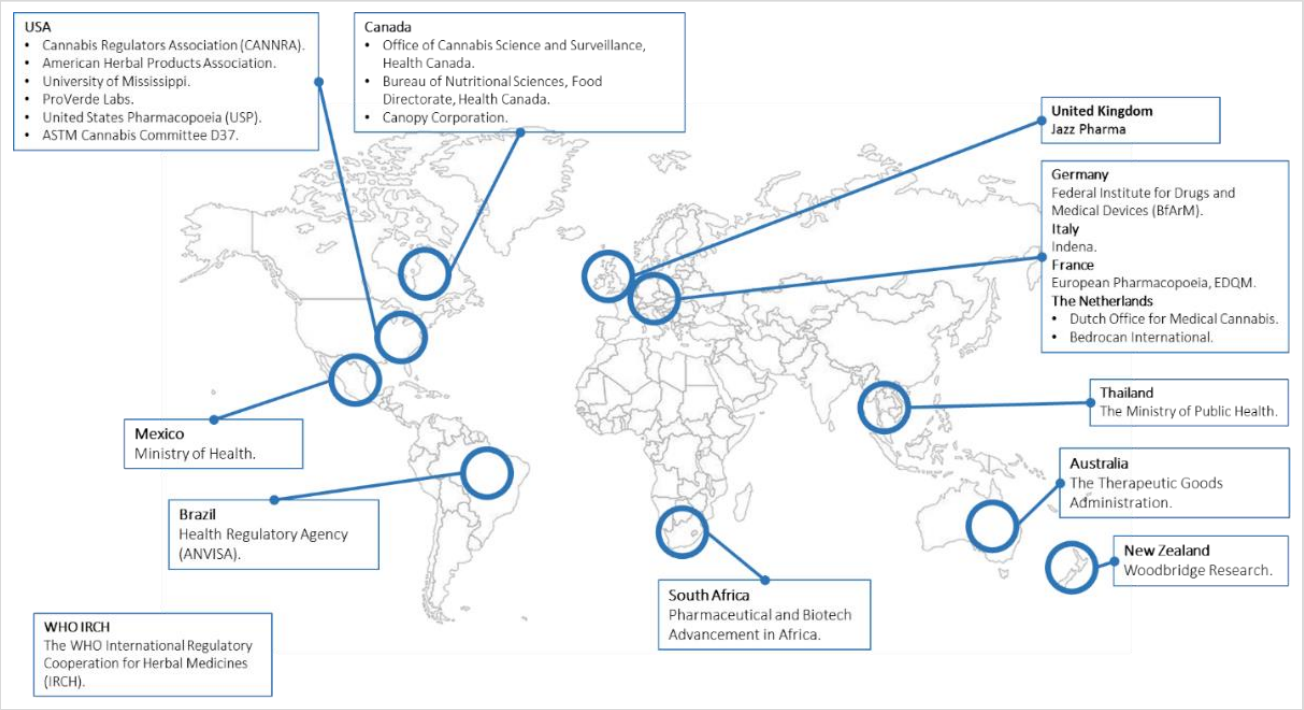
More than 300 global delegates discussed the purpose of alignment of quality standards and good practices as well as the impact on industry, regulatory agencies, and laboratories worldwide.

Workshop Objectives:

- Discuss the findings and themes identified during the first workshop and understand the impact at the global level.
- Identify global data gaps to inform future research and the scientific basis for the development of standards and practices.
- Explore the potential for alignment among standards organisations and government regulators across the globe.

Workshop session chairs and presenters

Schematic: Regions and organizations represented at the workshops.



Regulatory

Session Chair and Speakers:

Julio Sánchez y Tépoz, former Head Commissioner of COFEPRIS, Ministry of Health, Mexico. (Session Chair).

Werner Knoess, Federal Institute for Drugs and Medical Devices (BfArM), Germany.

Joao Perfeito, Health Regulatory Agency (ANVISA), Brazil.

Andrew Wayne, Office of Cannabis Science and Surveillance, Health Canada, Canada.

Jenny Burnett, Manufacturing Quality Branch (MQB), Therapeutic Goods Administration, Australia.

Somsak Sunthornphanich, Bureau of Drug and Narcotic, Department of Medical Sciences, Ministry of Public Health, Thailand.

Industry

Session Chair and Speakers:

Holly Johnson, American Herbal Products Association, USA. (Session Chair).

Alan Sutton, Jazz Pharma, United Kingdom.

Giovanni Appendino, Indena, Italy.

Tjalling Erkelens, Bedrocan, The Netherlands.

Marcel Bonn-Miller, Canopy, Canada.

Standards

Session Chair and Speakers:

Robin J. Marles, Bureau of Nutritional Sciences, Food Directorate, Health Canada, Canada. (Session Chair).

Jaume Sanz-Biset, European Pharmacopoeia (Ph. Eur.), EDQM, France.

Nandu Sarma, Director, Dietary Supplements and Herbal Medicines, USP. (Workshop Moderator)

Marco van de Velde, Dutch Office for Medical Cannabis, The Netherlands.

Charles Wu, The WHO International Regulatory Cooperation for Herbal Medicine (IRCH).

David Vaillencourt, Vice Chair, ASTM Committee D37 on Cannabis, USA. (Workshop Moderator)

Analytical / Laboratory

Session Chair and Speakers:

Martin Woodbridge, Woodbridge Research, New Zealand. (Session Chair and Workshop Moderator).

Mahmoud ElSohly, University of Mississippi, USA.

Chris Hudalla, ProVerde Labs, USA.

Remco Vree Egberts, Ofichem, The Netherlands.

Gillian Schauer, Cannabis Regulators Association, USA.

Appendix 2: Summary of workshop findings

The two workshops covered various issues which are summarised according to four themes, (i) Regulatory Practices, (ii) Standards and Practices, (iii) Monographs and Methods, and (iv) Laboratory and Analytical.

Theme 1: Regulatory Practices

Summary

All medicine regulators want to assure the quality, safety, the efficacy of medicines, including cannabis derived medical products.

1.1. The United Nations conventions and domestic regulations

The United Nations (UN) drug control conventions and the relationship to domestic regulations were discussed.
Acknowledging the potential therapeutic utility of *Cannabis sativa* L. and its active components, the regulatory framework for the medical and scientific use is defined within the UN drug control conventions. [3] The convention administrators, the UN International Narcotic Control Board (UN INCB), recently developed a global framework for cannabis licensing, monitoring and reporting among signatory nations. International alignment to this framework is essential to international agreements and transitional trade.

The quality of data for reporting by 'responsible national authorities' to the UN INCB is important to the legitimacy of domestic licensing and monitoring activities. A country submits annual national drug use estimates for medical and scientific use. They also report on the yields of domestic production (e.g., *cultivation or manufacture*) and domestic consumption. The accuracy of analytical laboratories and harmonisation of standards and practices is therefore important to all countries' licencing, monitoring and reporting activities. Quality assurance is also the basis of medicine regulators' mutual recognition agreements and the validity of cannabis as a medicine.

Good regulatory practice in the context of cannabis means 'national agencies'[4] can improve communications between themselves, to share best practices, and promote common approaches to import and export.[5]
In this regard, the adoption of a set of uniform definitions is desirable, including specifications for chemotypes of *Cannabis sativa* L.

1.2. Good Regulatory Practices

Variability across the globe includes different regulatory requirements on licensing of activities, certification, good practices and quality standards.

Regulators don't always incorporate a specific standards or good practices as a requirement. Despite that, standards and good practices are there to assist industry to demonstrate compliance and to produce quality medicines. Increased standardisation helps regulators assess and identify risks, and helps industry meet validation requirements for cannabis-derived materials and medicines.

Medicine regulators need to be able to apply regulatory controls, perform industry audits, and manage laboratories who undertake quality related tests. Additionally, national authorities are required to monitor

[3] The Single Convention on Narcotic Drugs, 1961 and The Convention on Psychotropic Substances, 1971 provide the regulatory framework for domestic legislation which controls the cultivation of cannabis plants, production and manufacture of, trade in, distribution, import and export, possession and use of narcotic drugs and psychotropic substances exclusively for medical and scientific purposes.

[4] With respect to 'national agencies' as per Article 28: Control of Cannabis, The Single Convention, 1961.

[5] 1961, article 4 (c): General obligations, and article 30, and article 31.

licensed activities, participate in international trade through export-import permits, and meet UN Convention reporting obligations (calculate cultivation and manufacturing yields, and report accurate quantities of controlled drugs utilized).

Finally, effective regulations prevent, or mitigate, the effect of the black market, which poses multiple threats to the regulated cannabis industry. [6]

In sum, good regulatory practices support industry, market development, and the availability of quality medicines.

1.3. Regulations

Domestic regulations provide a platform for government institutions, industry, and the health profession to define and manage the risk associated with materials and products containing controlled drugs.
Among the key drivers of domestic regulatory frameworks for cannabis-derived medicines is that patients with severe illness should have access to quality products prescribed by doctors.

A level of consistency is needed for industry to operate effectively and efficiently.[7]
Despite many similarities, key differences across the globe include requirements for labelling, [8] microbial testing, terpenoid content testing, and whether to use water activity or loss on drying to assess water content. Globally, there are inconsistencies in requirements for representative batch sampling and sample preparation, assay accuracy and the validation of test methods, and permissible contaminant limits, especially for pesticides.
Pesticide contamination testing is mandatory for cannabis. However, there are hundreds of available and commercially used pesticides. Therefore, it is necessary to understand the production processes and inherent risks of contamination for each product. A data source is needed globally.

It is well noted that botanical substances with multiple compounds are difficult to standardise. In some jurisdictions the cannabinoid assay batch release criteria has a ± 20 % deviation, some have moved to a level of ± 15 %, and some may be down at ± 10 % for the whole flower. The *Ph Eur*. has proposed a ± 10 % cannabinoid variance, while the USP suggested ± 20 %. There is discussion on whether ± 10 % or ± 20 % should apply to a medical product or to the herbal substance itself.

The challenges that analytical laboratories face is vast (see laboratory section). This is emphasized in U.S. State regulations compared to national approaches in most of the rest of the world. In the United States, laboratories have not been required to use pharmacopeial or consensus standards, which has resulted in dozens of unique regulatory frameworks and laboratories using different testing methods. It was well noted that regulators who adopt consensus standards and good practices reduce obstacles to effective regulatory control, the audit process and data collection, and the regulatory support of industry.

Regulators need to be equipped to perform the tasks needed within this industry to promote cannabis quality. This includes regulators that, among other things, can effectively audit and enforce licenced activities, detect laboratory-related issues, and promote the use of quality orientated monographs. Enforcement can be challenging because regulatory agencies may not have enough appropriately trained scientific staff, in particular, staff who can assist laboratories to validate methods and arbitrate lab-to-lab differences.

[6] The black market may attract patients to the unregulated market. The absence of quality standards poses significant risk to consumer safety. The prevalence of synthetic products on the market presents unknown hazards.

[7] For example, common quality control requirements which cover chemical and microbial contaminants analysis before batch release.

[8] Labelling according to medicine standards, including cannabinoids present. Industry is often required to characterise the complete makeup of the product, and quantify the contents and prove the consistency of the product. This includes such details as: the name of the product and its content, warning labels, any use requirements, and the manufacturer details.

Theme 2: Standards and Good Practices

Summary

Standards and Good Practices in the cannabis industry were discussed at length.

Industry development and the globalisation of trade means cannabis materials and medicines may be produced and distributed in complex, fragmented supply chains that cross borders. Standards and practices are therefore required for to ensure the quality and the traceability of the starting materials through to the finished products, especially when for medical and scientific use.

There are challenges and costs associated with bringing safe and quality cannabis-derived materials medicines to market, and for their global trade (import and export).

2.1. Standards

The significant challenge is in standardizing a botanical starting material, given the inherent heterogeneity of the cannabis plant. Standards and standardisation are important to ensuring consistency in batch-to-batch cannabinoid content (w/w) alongside a reproducible chemical fingerprint. This is required for effectively managing industrial contracts, meeting manufacturing input needs, and contractual agreements requiring supplier verification and audit. Examples of recent cannabis standards include those from ASTM Committee D37 and ISO; the USP Herbal Medicines Compendium (HMC) and EDQM / Ph Eur draft cannabis inflorescence monographs; the various national pharmacopoeias concerning cannabis-derived materials and medicines including Germany (2017), Denmark (2019), Switzerland (2019), Thailand, (2020), and the American Herbal Pharmacopoeia. Along with the Dutch cannabis quality monograph, and Australian and New Zealand cannabis quality standards.

Standards in cross-border trade are required for a highly functioning industry and for continuity of medicines access. Trade, in full compliance with the UN Single Convention on Narcotic Drugs, 1961, typically includes the import and export of cannabis-derived materials and medicines as per typical pharmaceutical industry rules and regulations – in particular, GMP. Domestically, regulators aim to establish an effective procedure for distribution; in multiple jurisdictions these procedures are compatible with rules for Good Distribution Practices (GDP) as is applied for registered pharmaceutical products.

Diverse and complementary standards are needed, but clear lines of communication must be maintained to prevent duplication or misuse of limited resources.
Global alignment of standards is fundamental to set specifications for identity, cannabinoid content, limits for contaminants, and other quality attributes. Additionally, standards are required to meet the challenges of un-validated test methods, inaccurate label claims for cannabinoid content, varying limits for microbial and chemical contamination, and emerging concerns related to synthetic minor cannabinoids and impurities. [9]

2.2. Practices

A Good Practice implies that strategies, approaches and activities undertaken have been shown through research and evaluation to be effective, efficient, sustainable and transferable, and to reliably lead to a desired result.

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[9] Documentary standards (i.e., pharmacopeial or compendial standards) articulate agreed-upon testing methods and acceptance criteria used in quality assurance and quality control protocols. These standards provide benchmarks to evaluate an article's identity, purity, strength, and performance. They provide transparency on quality expectations. They can be utilised by any stakeholder to help assess the quality of their products.

Reference standards are physical samples consisting of a known quantity of a substance or ingredient, developed in alignment with the specifications outlined in the corresponding documentary standard. These standards undergo rigorous testing in a collaborative study and are subject to statistical analysis. These standards come in small vials and enable manufacturers to test their product against the standards to ensure it meets published specifications.

Various options are proffered for industry for both production and quality control. From Germany to Brazil and Australia to Thailand, multiple countries require industry adherence to GMP for all medicine manufacture. For cannabis cultivation there is more variability.

Good Agricultural and Collection Practice (GACP) is the only set of requirements available to companies in the EU for the cultivation of medicinal cannabis. Because GACP alone is insufficient for cannabis flower intended for medical use by inhalation, a new cultivation standard is needed. This is used to increase the quality of cannabis cultivation and to approach GMP as closely as possible.

Trade is typically on the basis that organisations are appropriately licenced and certified as in compliance with, or abiding by applicable good practices, such as GMP and GDP.
Quality assurance is the basis of medicine regulators' mutual recognition agreements (MRA) with other regulators. However, variability as to the understanding of Good Practices for cannabis and their appropriate application in industry severely undermines the shared responsibility and applicability of MRAs.

Theme 3: Monographs and methods

Summary

Various monographs on *Cannabis sativa* L. inflorescence are proposed or have been implemented across the globe in official pharmacopeia. Compliance-orientated, quality-focused monographs improve regulators ability to audit, monitor and detect issues within laboratories and industry.

The development of robust, effective methods which are adopted by industry is required. These must be cost effective so that countries and organisations with limited resources are able to comply. A monograph must represent only those tests which are required to determine, for example, identity, potency and quality.

Science-based resources to address the common challenges and possible alignment of approaches across jurisdictions would serve to protect patients and promote research.

3.1. Inflorescence of *Cannabis sativa* L

Materials of botanical origin can be highly variable because their chemistry and morphology depends on genetic variation. This variation is amplified by differences in environmental growing conditions, and with variations in practices and conditions at harvest, drying and processing.

The qualitative and quantitative methods used to identify and quantify cannabinoids (and terpenes) in cannabis materials and derived products must be accurate, precise, reliable and affordable. [10] Additional methods to determine quality related attributes, to identify and quantify contaminants and impurities, must be applicable to botanical materials as *Cannabis sativa* L.

Given the inflorescence of *Cannabis sativa* L. is the foundation of industry and cannabis-derived medicines, it makes sense that harmonization starts here. A monograph on cannabis inflorescence would cover at a minimum: identification, assay for cannabinoid content, moisture content, and contaminants (foreign matter, microbial, heavy metal, and pesticide content).

3.2. A global monograph

A globally adopted compliance-oriented monograph was discussed.

[10] The Limit of Quantification (LOQ) is the lowest analyte concentration that can be quantitatively detected with a stated accuracy and precision. The Limit of detection (LOD) is the lowest concentration that can be measured (detected) with statistical significance by means of a given analytical procedure.

All the represented nations either adopt a monograph and or use of validated methods from official pharmacopeias, including for establishing limits for impurities or contaminants, and for quality control testing of materials and medical products prior to release.

The pharmacopeial monographs [11] are the most reliable and accepted published methods for the analysis of materials and medicines. The U.S. Pharmacopeia (USP) and the European Pharmacopeia (Ph Eur.), for example, provide relevant information on quality attributes and risk-based testing. It was well noted that pharmacopoeia monographs are not stand-alone texts and must be read in conjunction with the General Notices, pertinent general texts and applicable general monographs. [12]

The general technical capacity of 'Competent National Authorities' to measure the quality and quantity [13] of controlled drugs is essential. Some nations may lack resources to effectively implement a laboratory control and testing program. [14] If resource availability and technical competencies at a national level are not available, reliance on industry Good Practices, Certificates of Analysis released by certified laboratories, Mutual Recognition Agreements, and a global cooperation on sharing knowledge is required. [15] At the national level, in many countries, chemical analysis down to low thresholds may not be possible given a lack of appropriate, cost-effective identification techniques, and because of available resources to achieve this long-term.

A globally accepted compliance-oriented monograph for cannabis would decrease risk at the government and industry level, while aiming to eliminate methods which may increase variation. Such a monograph must consider the factors of cost (affordability), value (fit-for-purpose: practical, applicable and reliable), and adoption (taken up by industry and regulators around the globe).

Theme 4: Analytical / Laboratory

Summary

Many more laboratories across the globe are now required to both qualitatively and quantitatively identify cannabis, and cannabis-derived material and products.

Analytical laboratories form an essential component of the production and supply chain, and quality assurance of cannabis-derived material and medical products. Like with other medicines, responsible and reliable analytical laboratories and monitoring programs are required. For government and forensic laboratories, this means:

- acting as the lead analytical proficiency laboratory (cross-laboratory validation),
- acting as an independent laboratory in disputes about medicine quality or label claims,
- identifying and categorizing when it is a medicine.

There is a need for effective, competent and well-resourced regulatory authorities who can undertake laboratory audits and provide oversight for highly functioning industries and markets.

Currently, there are large variances in jurisdictional requirements for analysis, alongside variable sample selection and preparation methods, issues with sample homogeneity, and inconsistencies in pesticide and

[11] Pharmacopoeia tests are reference methods based on the latest scientific knowledge, and which are essential in cases of dispute.

[12] For example, within Europe and among jurisdictions that adopt Ph Eur monographs, of particular importance for the draft cannabis flos monograph is where the following interact: *Ph Eur.* 1433 Herbal drugs, *Ph Eur. 20813* Pesticide residues, *Ph Eur. 20802* Foreign matter, *Ph Eur. 50108* Microbiological quality of herbal medicinal products for oral use and extracts used in their preparation, and *Ph Eur. 50104* Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use.

[13] As per the requirements of the UN Convention on Narcotics Drugs, 1961.

[14] The implementation of such a framework at the national level is hindered because chemical analysis to the thresholds indicated may not be possible given a lack of appropriate identification techniques. It may also not the best use of national resources.

[15] These aspects are essential to support the quality framework implemented by a Competent National Authorities.

microbial contaminants testing. Additionally, there are reports of lab-to-lab variability in results, and the complex issue of 'laboratory shopping' for the best assay results in some jurisdictions.

4.1. Certifications and audit

Industry needs to have contractual quality agreements that specify the quality standards that must be applied to testing. This requires laboratories to take part in supplier qualification programmes and audits.
A minimum requirement for laboratory licensing, certification, and quality-assurance audits is required.

4.2. Validation

Variation in instruments and by laboratory personnel will introduce a small amount of variability, which is amplified with lab-to-lab differences. This is an issue identified for cannabis. Eliminating intra- and inter-laboratory variation is a priority, given this issue currently confronts both industry and regulators.

Monographs contain validated procedures. However, variation occurs with the instruments, and laboratory personnel, with each introducing a small amount of variability. This can be amplified with lab-to-lab differences. This is especially an issue identified for the analysis for cannabis materials. Therefore, to achieve consistently reliable results, accredited laboratories require cross-laboratory validation to confirm that comparable data is generated across multiple laboratories using the same methods. Participation in external proficiency testing programs is mandatory under both GMP certification and ISO 17025 accreditation. [21] An approved laboratory may act as the lead in cross-laboratory validation process. [16]

A lead laboratory in cross-laboratory validation process is required for individual countries. This laboratory provides external quality-control assurance testing of identical samples in a variety of laboratories to compare results. Standardized methods and proficiency testing will help to address many of the identified challenges. The ultimate goal would be for global harmonisation of standards.

4.3. Sampling and sample preparation

Harmonisation of sample selection and sample preparation methodology is critical and is currently a major issue.

Sampling should consider the distribution of the compounds across the cannabis plant and herbal material representing the batch. The sampling procedure must not be deliberately manipulated to obtain the most or least 'potent' material. Strict protocols are needed as the quality of the sample is additionally affected by the production environment (greenhouse and other indoor) and preparation situations (time, light, moisture).

The homogeneity of the sample being tested is essential. Reducing the particle size of the dry cannabis herbal material without affecting the nature of the analytes can be difficult. Pulverising and sieving cannabis material may lead to significant loss of active components by the sticking of glandular trichomes to sieves, blenders, cutters, etc. This is particularly so with high potency cannabis strains.

Sampling and sample preparation protocols (descriptive information) for industry sample collection, the submission to laboratories, and the sample preparation procedures for testing is needed.

4.4. LoD vs a_w

Moisture / water content of cannabis inflorescence can result in microbial growth, affecting the quality and safety of the material.

[16] A proficiency testing programme is a standard procedure in the analytical testing industry for external quality-control assurance, in which identical samples (i.e. homogenised cannabis sample with a defined cannabinoid content) are sent to a variety of testing facilities in order to compare results.

A guidance text on the principles and practice of validating tests is available through the ICH Harmonised Tripartite Guideline Validation of Analytical Procedures: Text and Methodology Q2 (R1). The guideline identifies the validation parameters needed for a variety of analytical methods.

Two methods for determining moisture / water content of cannabis inflorescence include Loss on Drying (LoD) and Water Activity (a_W).

Ana_W between 0.60 ± 0.05 is applied to cannabis herbal material to prevent degradation from excessive drying (below 0.55 a_W) or microbial growth (above 0.65 a_W). Water activity has not been widely used in the medico-scientific industry for cannabis materials.

LoD is used to determine the moisture content and to calculate the cannabinoid content on a weight for weight basis (e.g., % THC w/w). This quantitative data is used for industrial contracts and licensing.

LoD is widely used in the medico-scientific industry for cannabis material (herbal substances) which constitute all or part thereof the material or product (i.e. inflorescence, leaves, resin extract or derived product). [17] [18] Noting that Ph. Eur. 2.2.32: Loss-on Drying measures the total change in weight of a material when the sample is dried (all volatile components). The Karl-Fischer method may not account for other volatile substance, such as terpenes (all volatile components), which constitute the total weight of the cannabis material sample. [19]

The adjustment for LoD recognizes the actual and potential for loss of those components. A loss will affect the weight of the sample, and thus the calculation of cannabinoids on a weight for weight basis (e.g., % THC w/w). The method used to determine LoD should reflect the actual content of cannabinoids in the material. Typically, a representative amount of sample is weighed, then the sample is dried. After drying, the sample is measured by dry weight. The difference between the two weights is the moisture content by weight. Typically, a limit of NMT 10% w/w is applied.

The most appropriate method is still requires further investigation. In the meantime, it is necessary to undertake analysis of a standardised reference cannabis material, over numerous batches, to determine the comparability of the two methods.

Contaminants

Pesticides are a major contamination risk. There are hundreds of available and commercially used pesticides, and the risk of contamination differs between indoor (controlled) and outdoor (uncontrolled) growing environments. When cultivating outdoors, in particular, there are not only challenges around pesticides, but also microbial, heavy metal and residual solvents contamination. All these contaminants can be equally inhomogeneous in their concentration throughout the collected sample.
Therefore, it is necessary to understand the production processes and inherent risks of contamination for each product. A data source and a pesticide testing framework are needed. The best framework is still to be determined – a risk-based matrix, a screening matrix, or a hybrid solution.

4.5. Certificate of Analysis

Industry and regulatory authorities around the world are challenged by analytical inconsistencies (e.g., irregular lab practices, inconsistent analytical methods, variable quality reference materials and in the samples and sample preparations.

The variability in the capacity of analytical laboratories presents challenges the validity of Certificates of Analysis (CoAs). Indeed, in some circumstances it is difficult to determine if the CoA is a true reflection of the batch and the quality of the material or product it represents.

[17] Refer to Ph Eur. 2.2.32: LOD for herbal drugs and Ph Eur. 2.8.16. Dry residue (liquid extract).

[18] For herbal drugs containing more than 10 ml/kg (1 %) of essential oil, the determination of water by distillation (Ph Eur 2.2.13) is carried out instead of the test for loss on drying. Many high potency cannabis chemovars may fall in this category.

[19] Ph Eur 2.2.32: Loss-on Drying measures the total change in weight of a material when the sample is dried (all volatile components), Karl Fischer Titration measures only water content (water-specific), Halogen Moisture Analysis (all volatile components).

Karl-Fischer determination: on 0.500 gram of the powdered drug [sieve number ca. 5mm] by heating for 24 hours at 40°C above diphosphoros pentoxide R under vacuum (1.5 – 2.5 kPa).

A uniform Certificate of Analysis, issued by proficient, validated laboratories for batch identification, traceability and quality is required to overcome this situation. The CoA would correspond to information to the label of the material and medicine. This CoA, at a minimum, would contain information about the cannabinoids present, characteristics of the makeup of the product, and quantify the contents and prove the consistency of the product.

4.6. Essentials of identification and analysis

A number of pertinent questions arose around technical discussions on quality control, identification and analysis which need further insight. Pressing questions include:

- *What is the best and most effective analytical procedure:*
    - *Is high-performance thin-layer chromatography (HPTLC) required? Identification by HPTLC chromatogram for Δ9-THCA than Δ9-THC, and for CBDA than CBD.*
    - *Identification by HPTLC-UV procedure?*
- *What are appropriate reference substances, i.e. cannabidiol for cannabis CRS (for quantitative use only) and cannabis flower for system suitability HRS (for qualitative use only).*
- *Assay:*
    - *What is the suitability test acceptance criteria, based on the chromatographic separation of acidic and neutral cannabinoids?*
    - *How to quantify CBN, i.e.., system suitability test acceptance criteria. Reference based on the separation of three different chromatographic pairs due to CBG and CBDA, CBGA and Δ9-THC, as well CBNA and CBC.*
- *What is the definition of foreign matter in herbal substances and herbal products, ies., classification of foreign material.*
- *Are microscopic tests required for each batch?*
- *Stability:*
    - *What stability tests are undertaken for the drug substance and product, including defining storage conditions, intermediate conditions, long-term stability, and photo stability testing requirements?*
    - *What stability studies requirements are needed to provide information on concentration ranges, manufacturing processes, compound stability and interactions with excipients, and extractables and leachables in finished products?*

Additional scientific investigation is required to address these questions.