



# Regulators Panel

Brazilian Health Regulatory Agency - ANVISA

João Paulo Perfeito  
December 7<sup>th</sup> 2022



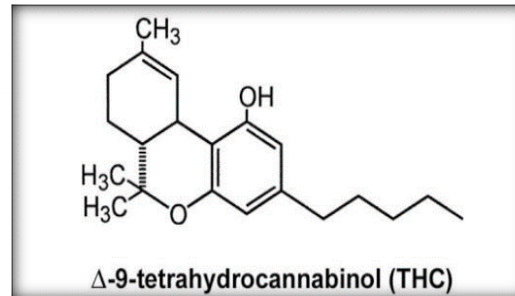


# Legislation related to controlled substances

- Cannabis plant and all derivatives are prohibited, except for restricted medical use and scientific purposes.
- Smoking, food or cosmetic uses are not allowed.



1961 Convention (DECREE No. 54.216 / 64) "Prohibit (...) **except for medical and scientific purposes**, under the direct control and supervision of the member country."



1971 Convention (DECREE No. 79.388 / 77) "Prohibit all types of use of these substances, **except for scientific purposes and very limited medical purposes** "

Law 11.343/2006  
Establishes the National system of public policies on drugs.  
Throughout the national territory, drugs are prohibited, as well as the cultivation, harvesting and exploitation of plants and substrates from which drugs can be extracted or produced, **except in the event of legal or regulatory authorization.**





# Cannabis access pathways

**License as medicines**  
(RDC nº 24/2011 or RDC nº 26/2014)

Herbal medicines	Specific medicines
RDC nº 26/2014	RDC nº 24/2011
The drug obtained from herbals as active raw materials, in any form, except for isolated or purified substances	“Phytopharmaco” – isolated or purified herbal substance



**Import for personal use**  
(RDC nº 660/2022)



# Anvisa improving access

- Improve population's access to cannabis-based medical products;
  - Channel for clarifying doubts from consumers and prescribers;
    - Monitoring and pharmacovigilance;
  - Commercialization of products with adequate quality for use; and
  - Availability of adequate product information to patients and prescribers.
- Discussion based on benefit x risk relationship, providing for the authorization of products that follow all technical requirements applied to medicines, except for the complete safety and efficacy dossier.





# Resolution RDC nº 327/2019

- Definition of a new class of product, other than medicine;
- Cannabis-based Product – manufactured product, intended for medical purposes, but without therapeutical claims, containing as active ingredients exclusively herbal preparations or isolated/purified substances of *Cannabis sativa*, including varieties and subtypes;
- “Sanitary Authorisation (SA)” – Simplified licensing of products;
- Non extendable licensing period of 5 years – after that – license as medicine;
- Need to meet all medicines requirements, such as quality attributes and GMP, except for complete safety and efficacy data.



# Cannabis-based products

## Resolution RDC nº 327/2019

- Prescription under doctor's responsibility and when other medicines are not available;
- Use only by oral and nasal route, in immediate release dosage forms;
- Compounding medicines are not allowed;
- Cosmetics, inhalation products, health related products and food are not allowed.



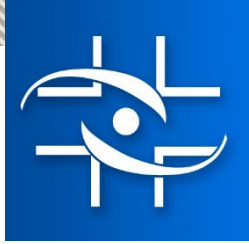
# Cannabis-based products

## Resolution RDC nº 327/2019



- Cultivation is not allowed. Need to import the herbal extracts or purified/isolated substances;
- Different selling controls according to the THC quantity ( $\leq$  or  $> 0,2\%$ );
- Standardized information for labeling and package leaflet (CBD and THC quantities).





# Requirements for Authorisation

- Quality dossier, including methods, specifications and results (analytical methodology validation - RDC nº 166/2017 and ICH Q2);
- Stability tests in climatic zone IVb (RDC nº 318/2019 and ICH Q1A – Q1F);
- Technical and scientific rationale that justifies the formulation and route of administration;
- Company must have operational conditions to carry out quality control analyzes in Brazil;
- GACP: plant supplier self-declaration validated by the company responsible for SA application;
- GMP (PIC/S)/ or Good distribution and storage practices and special authorisation for controlled medicines (AFE);
- Company must have ability to receive and handle notifications of adverse effects and technical complaints; and
- Benefit-risk assessment plan.

**RDC nº 327/2019**







# Quality Control (QC)



- Cannabis-based products must follow all medicines quality requirements:
  - Herbal medicines (RDC nº 26/2014) / Isolated substance of herbal origin (RDC nº 24/2011);
- Finished product: QC must be carried out in the national territory for all imported batches;
- In case of monograph in official pharmacopoeia, this monograph becomes mandatory.

Coming soon - Brazilian Pharmacopoeia: *Cannabis sativa* L. inflorescence monograph.



# Official Pharmacopoeias in Brazil



Brazilian Pharmacopoeia 6th Edition published in 2019 + RDC nº 511/2021

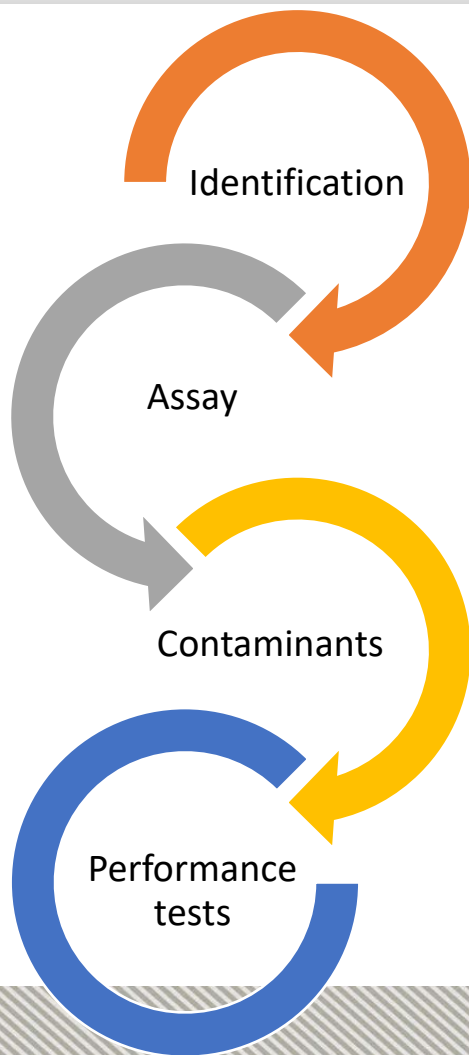
- German Pharmacopoeia;
- United States Pharmacopeia;
- Argentinean Pharmacopoeia;
- British Pharmacopoeia;
- European Pharmacopoeia;
- French Pharmacopoeia;
- International Pharmacopoeia;
- Japanese Pharmacopoeia;
- Mexican Pharmacopoeia;
- Portuguese Pharmacopoeia.

English version for free: <https://www.gov.br/anvisa/pt-br/assuntos/farmacopeia/farmacopeia-brasileira>





# Herbal Medicines QC



## Raw materials (Herbal substance and Herbal preparations)

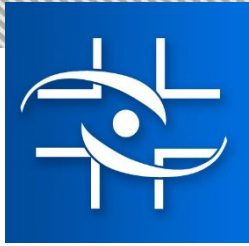
- Identification
- Assay
- Contaminants
- Phisico-chemical tests

## Excipients and packaging materials

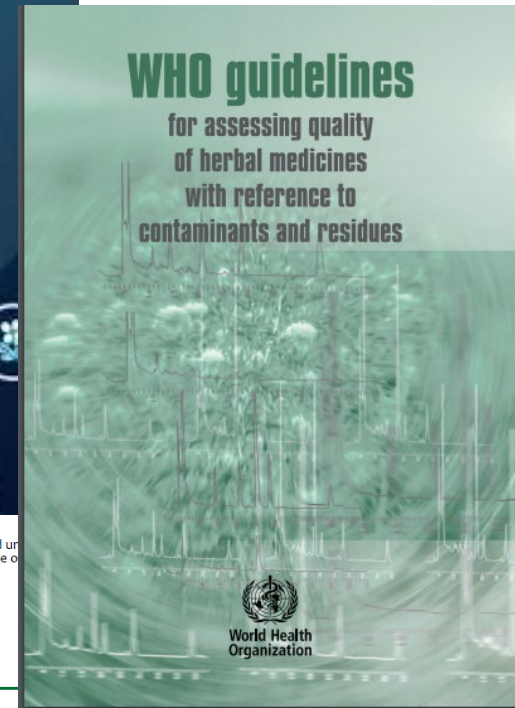
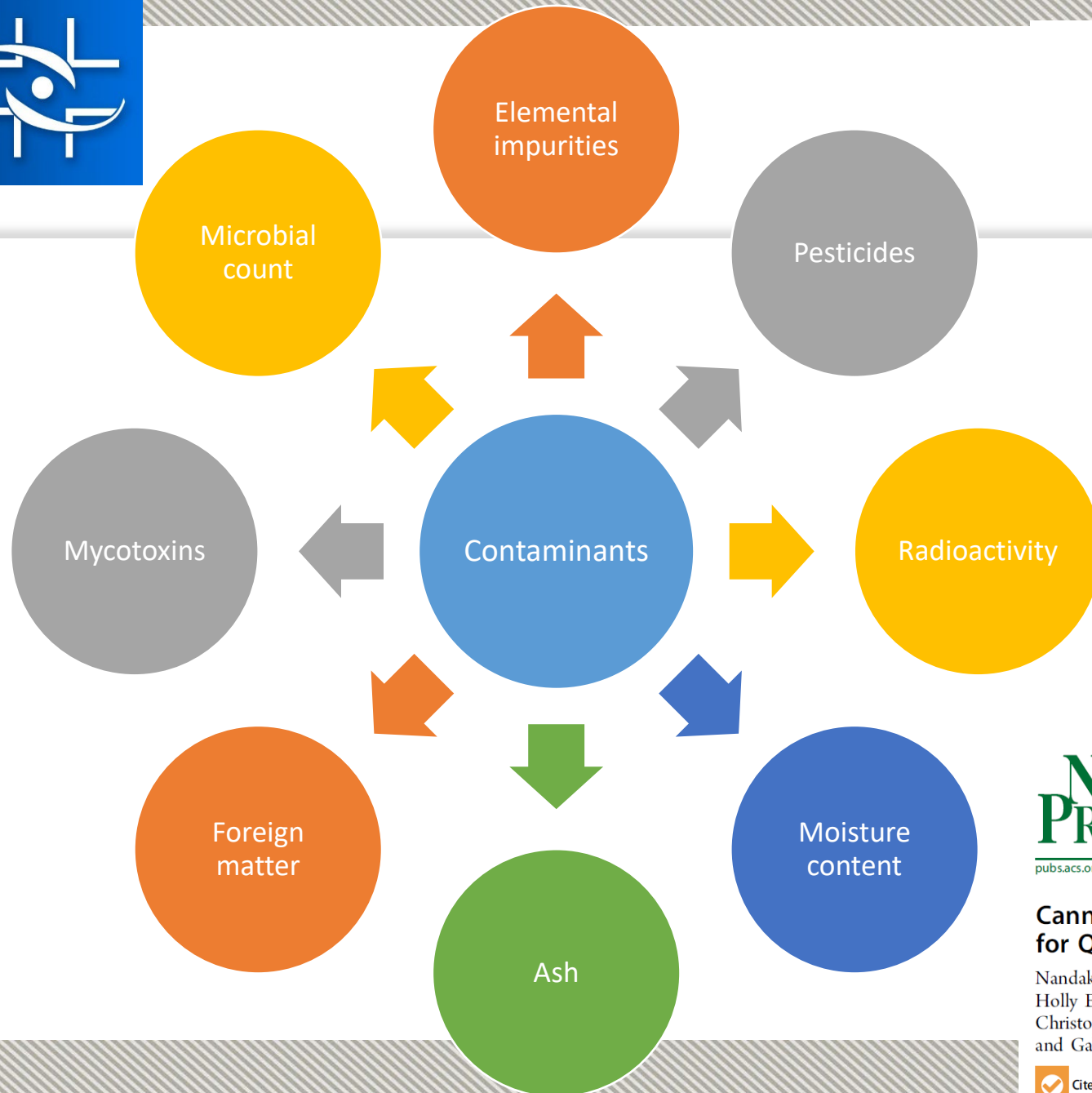
- Identification
- Assay
- Contaminants
- Control of excipient of animal origin
- Packaging specifications

## Finished products

- Identification
- Assay
- Specific tests according to the dosage form
- Stability



# Contaminants



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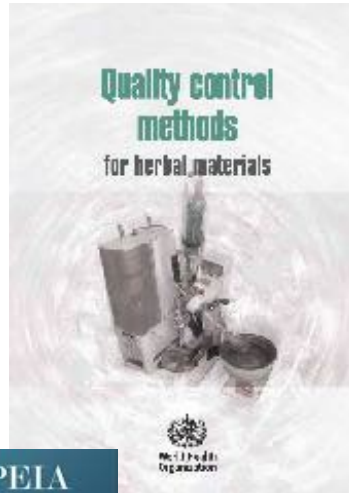
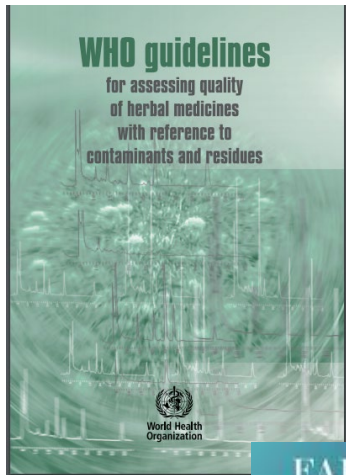
## Cannabis Inflorescence for Medical Purposes: USP Considerations for Quality Attributes

Nandakumara D. Sarma,\* Andrew Wayne, Mahmoud A. ElSohly, Paula N. Brown, Sytze Elzinga, Holly E. Johnson, Robin J. Marles, Jeremy E. Melanson, Ethan Russo, Lawrence Deyton, Christopher Hudalla, Gordon A. Vrdoljak, Joshua H. Wurzer, Ikhlas A. Khan, Nam-Cheol Kim, and Gabriel I. Giancaspro





# Mycotoxins and Pesticides



*“Mycotoxins comprise four main groups, namely, **aflatoxins, ochratoxins, fumonisins and tricothecenes**, all of which have toxic effects. Aflatoxins have been extensively studied and are classified as Group 1 human carcinogens by the International Agency for Research on Cancer .”*



*“Mycotoxins and, when appropriate, endotoxins should be tested for using an appropriately validated and sensitive method, and amounts should be below the limits set in national or regional standards.”*

Pesticide residues Brazilian Pharmacopoeia (same content as the European Pharmacopoeia).



# Isolated substances of herbal origin QC

- Substance quality report, including minimum requirements for identity and quality, according to official pharmacopoeias or scientific references;
- Details on the extraction process, substances purification or isolation methodology; equipment, solvents and excipients, if applicable.



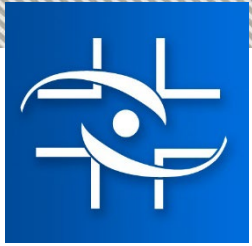




# Stability tests



- For the drug substance and product;
  - Accelerated storage conditions;
  - Intermediate conditions;
  - Long term stability;
  - Photostability testing.
- 
- RDC nº 318/2019
  - ICH Q1A(R2) - Stability Testing of new Drug Substances and Products;
  - ICH Q1B – Photostability Testing of new Drug Substances and Products.
- 
- The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a re-test period for the drug substance or a shelf life for the drug product and recommended storage conditions.



# Analytical Monitoring Program

- Systematically monitor analytical QC data of Cannabis-based products sent to Anvisa by the responsible analytical laboratories;
- Carry out guidance and fiscal analyzes on samples of Cannabis-based products and medicines containing CBD and THC (INCQS – Brazilian official QC laboratory);
- Forward Analytical Reports produced to the competent authorities to support relevant health actions;
- Publicize analytical results obtained, as well as the health actions adopted by Anvisa.

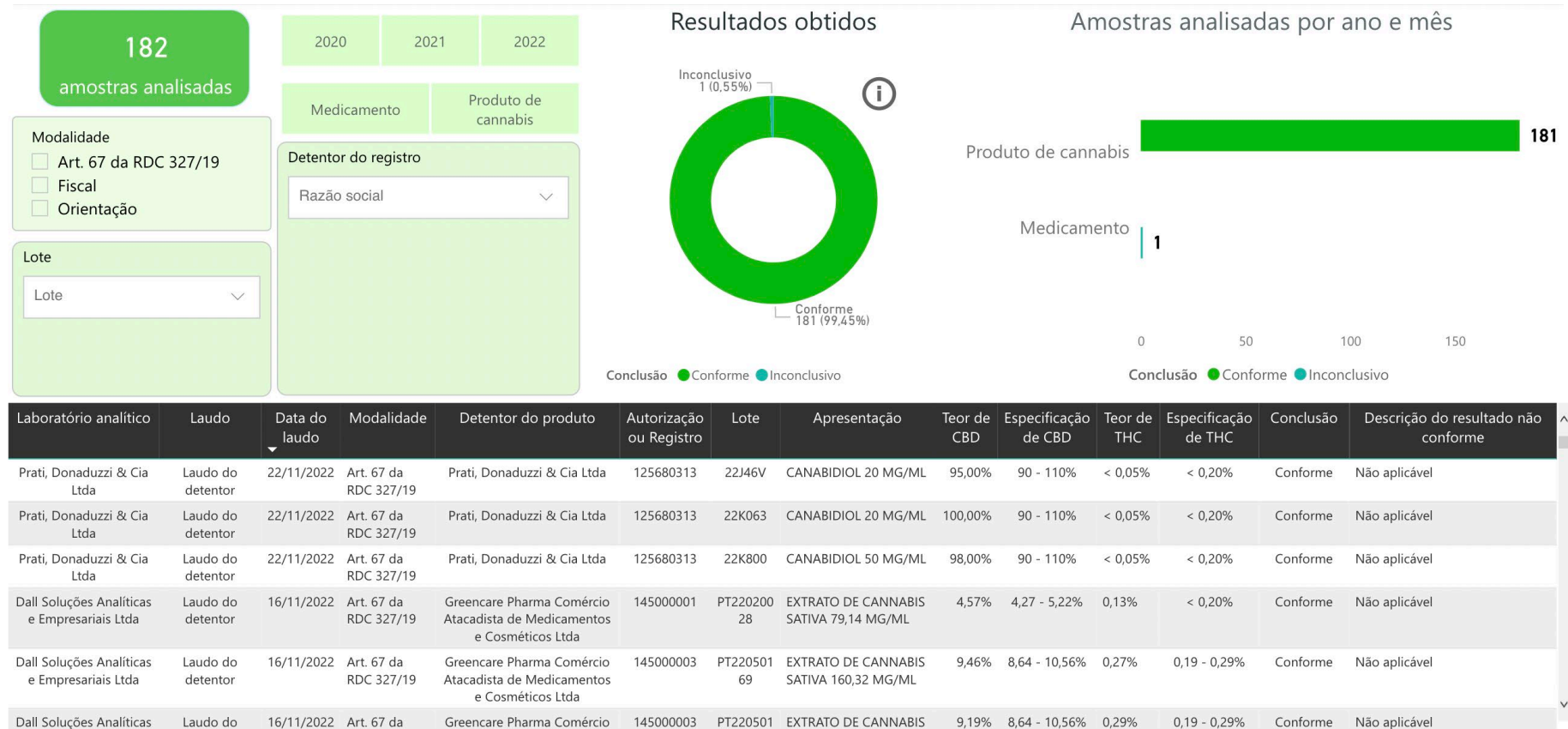






# Analytical Monitoring Program

From March 2020 to November 2022, Anvisa obtained analytical data from 182 batches.



<https://shre.ink/1Q9V>



# Technical assessment - Anvisa's experience

Main quality reasons for on demands after technical assessment:

- Process for obtaining API and product incomplete/without the necessary detailing;
- Inadequate API classification: herbal preparation or isolated/purified herbal substance;
- QC tests and specifications incomplete, without reference or inadequate definition of acceptance criteria (e.g., tests for pathogens);
- Stability tests, specifications, frequency and conditions inadequate;
- GMP not complying manufacturer (dietary supplements manufacturer or other);
- Outsourced QC activities (unclear responsibility of third party contracted and non proof of qualification for the specific activity to be conducted).







# Future Perspectives



- Improvements as a continuous process.
- Review of Resolution RDC nº 327/2019:
  - Art. 77 → The guidelines established for Sanitary Authorisation are transitory.
  - **The Resolution shall be reviewed within 3 years after publication.**
- Results related to research advances and the evolution of scientific knowledge;
- The experience accumulated in the last 3 years;
- Global regulatory maturity on the subject;
- Contribution from stakeholders: scientific community, health professionals, patients, manufacturing companies, society ...



# Thank you!

## **Brazilian Health Regulatory Agency Agência Nacional de Vigilância Sanitária**

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