NORMATIVE INSTRUCTION – IN N. 39, DATED AUGUST 21, 2019

Provides on the Good Manufacturing Practices complementary to Phytotherapeutic Medicines.

The Collegiate Board of the National Sanitary Surveillance Agency, in the use of the attribution conferred by art. 15, III and IV allied to art. 7º, III and IV of Law N. 9,782 of January 26, 1999, and to art. 53, VI, §§ 1 and 3 of the Internal Regulations approved by the Resolution of the Collegiate Board of Directors - RDC N. 255, of December 10, 2018, at a meeting held in XX of XXXX of 201X, resolves:

CHAPTER I
INITIAL PROVISIONS

Section I
Objective

Art. 1. This Normative Instruction has the objective of adopting the guidelines of Good Manufacturing Practices of Phytotherapeutic Drugs of the Scheme of Cooperation in Pharmaceutical Inspection, PIC/S, as complementary requirements to be followed in the manufacture of phytotherapeutic medicinal products in addition to the General Guidelines of Good Manufacturing Practices for Medicines.

Section II
Scope

Art. 2. This Normative Instruction applies to the companies that carry out the operations involved in the manufacture of phytotherapeutic drugs, experimental drugs.

Art. 3. This Standard Instruction also applies to all phytotherapeutic raw materials, including medicinal plants, plant drugs and phytotherapeutic preparations.

CHAPTER II
GENERAL PROVISIONS

Section I
Introduction

Art. 4. Due to their complex and variable nature, the control of raw materials, storage and processing must assume a certain importance in the manufacture of phytotherapeutic medicinal products.

Art. 5. The raw materials used in the manufacture of a phytotherapeutic medicinal product may be medicinal plants, plant drugs or phytotherapeutic preparations.

Paragraph 1. The plant drug must be of comparable quality to its use and supporting data should be processed to the manufacturer of the preparation or the phytotherapeutic drug.

Paragraph 2. The guarantee of the consistent quality of the plant drug must pass through the acquisition of information of its agricultural production.

Paragraph 3. Cultivation and harvest regulations should be followed.

Section II
Applicability

Art. 6. The applicability of Good Manufacturing Practices to the phytotherapeutic medicinal product and its raw materials depends on the processing stage.

Art. 7. Depending on the stage, the regulation of agricultural activity, good practices for the manufacture of pharmaceutical inputs or good manufacturing practices may be applied.

Art. 8. Annex 1 determines the applicability of each regulation according to the processing stage.

CHAPTER III
SPECIFIC PROVISIONS

Section I
Facilities

Subsection I
Storage Areas

Art. 9. The plant drugs must be stored in areas separated

Art. 10. Storage areas should be protected with the entry of insects or other animals, especially rodents.

Art. 11. Effective measures should be taken to prevent the propagation of any of these animals and micro-organisms brought with the raw substance, to avoid fermentation or mold growth, and to avoid cross-contamination.

Art. 12. The quarantine plant drugs should be stored in a separate area of approved plant drugs.

Art. 13. The storage area should be well ventilated and the containers should be positioned in such a way as to allow the free flow of air.

Art. 14. Special attention should be given to the cleaning and good maintenance of the storage areas, especially when generating particles and dust.

Article 15. The appropriate storage conditions of plant drugs and phytotherapeutic preparations, such as special conditions of humidity, temperature or light protection, shall be provided and monitored.

Subsection II
Manufacturing Areas

Art. 16. Specific guidelines shall be provided during the operations of sampling, weighing, mixing and treatment of plant drugs and phytotherapeutic preparations, whenever dust is generated, in order to facilitate cleaning and avoid cross-contamination, such as the extraction of powders or the use of dedicated facilities.

Subsection III
Equipment

Art. 17. The equipment, filtering materials, among others, used in the manufacturing process must be compatible with the extraction solvent, in order to avoid any release or absorption undesirable for substances that may affect the product.

Section II
Documentation

Subsection I
Raw-materials Specification

Art. 18. Manufacturers of phytotherapeutic medicinal products shall ensure that they use only raw materials of vegetable origin manufactured in accordance with the Good Manufacturing Practices and the registration of the product.

Art. 19. Exhaustive documentation shall be made available on the audits of suppliers of raw materials of vegetable origin conducted by or on behalf of the manufacturer of the phytotherapeutic medicinal product.

Sole paragraph. Audits for the active components are critical to the quality of the raw materials.

Art. 20. The manufacturer shall verify, where appropriate, whether the suppliers of the plant drug comply with the relevant agricultural regulations and, if not, apply appropriate controls in accordance with Quality Risk Management.

Art. 21. In order to comply with the general guidelines of good manufacturing practices set forth in the specific regulations, the documentation referring to the plant drugs and their preparations should include:

I. Official botanical nomenclature (genus, species, subspecies / variety and author) and other relevant information, such as cultivar and chemotype, must be provided;

II. Details of the origin of the plant (country or region of origin and, where applicable, crop, harvest time, collection procedures, possible pests used, possible radioactive contamination, among others);

III. Part (s) of the plant (s) used;

IV. The drying system, a dried plant is used;

V. Description of the plant drug based on macroscopic and microscopic visual examination;

VI. Suitable identification tests including, where appropriate, identification tests for constituents with known therapeutic activity, or specific markers and tests when a plant drug is likely to be adulterated / replaced. Authentic reference copy must be available for identification purposes;

VII. Determination of water for plant drugs, obtained according to the relevant Pharmacopoeia;

VIII. Content of constituents with known therapeutic properties or, where appropriate, markers;

IX. Appropriate methods to determine possible contamination and limits of pesticides accepted in accordance with relevant methods of the Pharmacopoeia or, in the absence thereof, with a properly validated method, unless otherwise justified / where applicable;

X. Tests to determine fungal and / or microbial contamination, including aflatoxins, other mycotoxins, pest infestations and their limits of acceptance, where applicable;

XI. Tests for heavy metals and for possible contaminants and adulterants, when applicable;

XII. Investigation of strange matters, when applicable;

XIII. Any other additional test according to the general monograph or specific monographs of the Pharmacopoeia for the peer material of vegetable origin, when applicable.

Art. 22. Any treatment used to reduce microbial, fungal, or other contamination must be documented.

Sole paragraph. Specifications and procedures including process details, tests, and residue limits should be available.

Subsection II
Manufacturing Instructions

Art. 23. The manufacturing instructions shall describe the different operations performed on the plant drug, such as cleaning, drying, grinding and sifting, including drying times and temperatures, and the methods used to control cut size or particle size.

Art. 24. Written instructions and records shall be provided to ensure that each container of plant drug has been carefully examined for any adulteration / substitution or presence of foreign bodies, such as metal or glass, parts of animals or excrement, stones, sand, among others, in addition to signs of deterioration and decomposition.

Art. 25. Manufacturing instructions shall describe safety screening or other methods of removal of foreign materials and appropriate procedures for cleaning / screening plant material prior to storage as an approved plant drug or prior to commencement of manufacture.

Art. 26. For the manufacture of phytotherapeutic preparations, instructions should include details of the solvent, time and temperatures of extraction, details of any concentration steps and methods used.

Section III
Quality Control

Subsection I
Sampling

Art. 27. Considering that medicinal plants or plant drugs are of a heterogeneous nature, sampling must be carried out by a person duly trained and with an appropriate procedure where each batch must be identified by its own documentation.

Art. 28. A reference sample of the vegetable raw material should be kept, especially in cases where the vegetable drug is not described in Pharmacopoeia.

Sole paragraph. Non-milled samples of the vegetable raw material are required when powdered in the subsequent manufacturing process.

Art. 29. Quality Control personnel must have specific knowledge and experience in plant drugs, phytotherapeutic preparations and phytotherapeutic medicinal products in order to be able to perform identification tests and be able to recognize adulteration the presence of mechanical growth, infestations or lack of uniformity in the raw material.

Art. 30. The identity and quality of plant drugs, phytotherapeutic preparations and phytotherapeutic medicinal products shall be determined in accordance with current national or international guidelines on the quality and specifications of phytotherapeutic medicines and, if applicable, monographs of specific pharmacopoeias.

Chapter IV
Final Provisions

Art. 31. Non-compliance with the provisions set forth in this Normative Instruction constitutes a sanitary infraction, under the terms of Law nº. 6,437 of August 20, 1977, without prejudice to civil, administrative and criminal liability.

Art. 32. This Instruction Normative comes into force 45 days after its publication.

WILLIAM DIB
CHIEF EXECUTIVE OFFICER

ANNEX
Table illustrating the application of good practices to the manufacture of phytotherapeutic medicinal products

Activity	Good Agricultural and Harvest Practices	GMP of Active Pharmaceutical Ingredients	General Guidelines on GMP of Drug
Culture, collection and harvesting of plants, algae, fungi and lichens and collection of exudates.			
Cutting and drying plants, algae, fungi, lichens and exudates *			
Cold pressing extraction of plants and distillation**			
Grinding, exudate processing, plant extraction, fractionation, purification, concentration or fermentation of herbal substances.			
Additional processing into a pharmaceutical form, including packaging as a medicine.			

Explanatory Notes:
GMP classification of plant material, depends on its intended use by the holder of the operating authorization. The material can be classified as active substance, intermediate or finished product. It is the responsibility of the manufacturer to ensure that the appropriate GMP classification is applied.
*Manufacturers should ensure that these steps are performed in accordance with according to the registry. For those initial steps that take place in the field, such as justified in the registration, national or international regulatory agricultural activity apply. GMP are applicable to additional cutting and drying.
**Regarding cold pressing extraction of plants and distillation, if it is necessary that these activities be an integral part of the harvest to maintain product quality within approved specifications, it is acceptable that they are carried out in the field provided that the cultivation complies with national or international regulation of agricultural activity. These circumstances shall be considered exceptional and justified in the relevant documentation of record. For field activities, documentation, control and validation appropriate in accordance with GMP principles should be ensured. The authority's regulators may carry out GMP inspections of these activities in order to assess the conformity.