# Quality Control and Standardization of Herbal Drugs

Quality control and the standardization of herbal medicines involve several steps. The source and quality of raw materials, good agricultural practices and manufacturing processes are certainly essential steps for the quality control of herbal medicines and play a pivotal role in guaranteeing the quality and stability of herbal preparations. For standard herbal drug production at industrial level, source herbal ingredients should be analyzed in detail in respect of quality, efficacy, performance and safety because drugs in commerce are frequently adulterated and do not comply with the standards prescribed for authentic drug. Quality refers to the status of a drug and is based on three important pharmacopoeial definitions such as identity, purity, and content of active constituents. Voucher specimens are reliable reference sources. Purity evaluation includes ash values, contaminants, heavy metals, microbial contamination, aflatoxins, radioactivity, and pesticide residues. Analytical methods, such as photometric analysis, TLC, HPLC, GC, MS or GS/MS, can be employed to establish the constant composition of herbal preparations. For content, sometimes markers can be used for control purposes because in most herbal drugs the active constituents are unknown. In other cases, where no active constituent or marker can be defined for the herbal drug, the percentage extractable matter with a solvent may be used as a form of assay. The choice of the extracting solvent depends on the nature of the compounds involved, e.g., hot water for herbal tea, steam distillation is suitable for essential oils. Complex nature of herbal drugs, unknown active principle, unavailability of selective analytical methods or reference compounds, chemical and natural variability in the plant materials as well as in source and quality of the raw material, methods of harvesting, drying, storage, transportation, and processing etc. are some of the problems that influence the quality of herbal drugs. Strict guidelines have to be followed for the successful production of a quality herbal drug. Standardization involves adjusting the herbal drug preparation to a defined content of a constituent or a group of substances with known therapeutic activity by adding excipients or by mixing herbal drugs or herbal drug preparations because botanical extracts made directly from crude plant material show substantial variation in composition, quality, and therapeutic effects. Standardized extracts are high-quality extracts containing consistent levels of specified compounds, and they are subjected to rigorous quality controls during all phases of the growing, harvesting, and manufacturing processes. Evaluation of crude drug means confirmation and determination of its identity, quality and purity and it can be done by several methods viz. organoleptic and microscopic evaluation; analytical determination of foreign matter, plant ash, heavy metals, microbial contaminants and aflatoxins, etc. Potentially hazardous contaminants and residues in herbal medicines may be grouped as chemical, biological, agrochemical residues, residual solvents, etc.

**Standardization of medicinal plant materials** is a determination of identity, quality and other features by their comparison with the standard requirements.

Because the active constituents of many natural drugs have been determined, chemical methods of evaluating crude drugs and their products are useful and, consequently, widely employed. For many drugs, the chemical assay represents the best method of determining the official potency. The application of typical physical constants to crude drugs is rare. However, physical constants are extensively applied to the active principles of drugs, such as alkaloids, volatile oils, fixed oils, and others.

The EU has in place two **Guidelines**concerning the quality of medicinal plants. One relates to the **Quality of Herbal Medicinal Products**, the other deals with the concept of **Good Manufacturing Practice (GMP)** as it is applied to the manufacture of those products. The World Health Organisation (WHO) has also published **Quality Control Methods for Medicinal Plant Materials** and as an integral part of its monographs on selected medicinal plants WHO includes a comprehensive quality monograph on each plant. In the EU’s Quality Guideline the initial control of the herbal drug involves a comprehensive specification for that drug. Ideally that monograph should be from a recognised Pharmacopoeia and increasing numbers of monographs on plant drugs now appear in the European and various national (particularly the US, French, German and Chinese) Pharmacopoeias. Other Pharmacopoeias such as the British Herbal Pharmacopoeia and various Homoeopathic (e.g. British and German) Pharmacopoeias are unofficial but contain valuable quality monographs.  Monographs usually include macroscopical and microscopical descriptions of the plant. Identification based on Thin—Layer Chromatography (TLC) and chemical assays are standard items in such monographs.

**The quality of medicinal plant materials**  is guaranteed by

l). registration and licensing system;

2). system of medicinal products evaluation (technological control departments and medicinal products quality control laboratories);

3). GMP (Good manufacturing practice).

**Standardization system in Azerbayjan**

Medicinal plant materials (or crude vegetable drugs) require adherence to obligatory standardization and certification.

According to The Law of **Azerbayjan** "On Medicines", state executive body in registration, manufacturing, evaluation and sale of medicines is the Ministry of Public Health in **Azerbayjan**. The special authorized body for medicinal products evaluation is the State Inspection for the Quality Control of the Medicinal Products. The State Scientific and Expert Center for medicinal products of the Ministry of Public Health of **Azerbayjan** and The Pharmacopoeia Commitee conduct registration of medicinal products. The former provides an expertise, the latter- preclinical and clinical drug investigations, approves normative and analytic documentation (Pharmacopoeia monographs and Temporary Pharmacopoeia monographs).

**Order of elaboration, compliance and approval of the analytic and normative documents on medicinal plant materials in Azerbayjan**

Creator of a new product provides a manufacturer with information that confirms perspectives of a new medicinal product encompassing results of scientific research of specific activity and project of the Temporary Pharmacopoeia monographs. The manufacturer presents experimental series of the product to certificate bases of the State Scientific and Expert Center for medicinal products of the Ministry of Public Health of Azerbayjan. According to these results the Center approves instructions for the use of the medicinal product. The Pharmacopoeia Committee approves the Temporary Pharmacopoeia monograph and informs the State Inspection for the Quality Control of Medicinal products. After the analytic and normative documents have been approved, the manufacturer produces 5 industrial series of a medicinal product and sends them for preliminary control to the State Inspection.

Permission for an industrial output and medicinal use is given by the Ministry of Public Health of Azerbayjan. The Ministry Bureau for registration of medicinal products recognizes a new product. Sales of medicinal products, medicinal plant materials and preparations as well,may be carried out provided that the certificate of quality issued by the manufacturers is made available.

**Standard Technical documents for MPM.**

A Pharmacopoeia monograph established requirements to a medicinal product, medicinal plant materials as well, as their package, conditions of preservation, methods, employed in evaluating medicinal products.

**Pharmacopoeia Monographs of the SPU (State Pharmacopoeia)**for medicinal plant materials comprise Latin names of plant material; nomination of used part; contents of active compounds; morphological and microscopic characters of MPM; chromatographic test for identity of markers; quality tests (foreign matter; loss on drying, or water content; total ash; ash insoluble in hydrochloric acid; extractable matter); techniques for quantitative determination of major active principles.

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### **In the past,**The analytic and normative documents (AND), **controlling the medicinal plant materials quality in pharmaceutical industry in Azerbayjan, were the Temporary Pharmacopoeia monographs and the Pharmacopoeia monographs.**

### **The Temporary Pharmacopoeia monographs were approved for the first industry series of new medicinal products for a period of 1 -3 years.**

All kinds of analytic and normative documents on medicinal plant materials in **Azerbayjan** were unified (according to ГOCT 42-Y-1-92)

**Pharmacopoeia Monographs** on medicinal plant materials or herbal collections comprised ingredients checklist (in case of herbal collections), Latin, Russian names of plant and family; the occurrence; microscopic analysis; test for identity; fracture (the character of broken surfaces); mass boundaries; pharmacologically active constituents or biological activity; moisture; ash; acid- insoluble ash; powdery; admixture of changed parts of the plant materials; impurities; foreign organic matter; package; labeling; transportation; conditions and time of preservation; the principal pharmacological activity. Number of document comprised category of the analytical and normative document, code of the Ministry of Public Health of Ukraine (42-Y), number of the monograph, code of organization (manufacturer), and year of approval.

**Standards**are defined as international, regional, national and *ГOCT* (in the Newly Independent States).

### **The analytic and normative documents, which regulate the medicinal plant materials in non-pharmaceutical industries, are State Standards, Technological Requirements, Branch Industry Standards of Ukraine.**

State Standard is registered by the State Standard Authority on almost all products in different branches of industry. Technical Conditions establish requirements to the particular production and regulate relations between a manufacturer and a consumer. Branch Industry Standard consists of additional technical requirements for manufacturing and distribution.

**Determination of identity and quality of medicinal plant materials according to Standard Technical documents**

**A batch of medicinal plant materials**is a quantity of crude drugs with the weight no less than 50 kg of the same official name, uniformed according to all characters, that have one document of quality. Each unit is examined for detection of damage and accordance of packing and labelling with requirements of Pharmacopoeia monograph.

For verification of accordance of quality of medicinal plant materials to requirements of Pharmacopoeia monograph an excerption from different parts of not damaged packages is to betaken. In the case of damaged packages each unit is opened.

**Sampling of material in bulk**

Inspect each container or packaging unit for conformity with pharmacopoeia monographs or other requirements regarding packaging and labelling. Check the condition of the package arx: note any defects that may influence the quality or stability of the contents (physical damage, moisture, etc.). Sample damaged containers individually.

If initial inspection indicates that the batch is uniform, take samples as follows. When a batch consists of five containers or packaging units, take a sample from each one. From a batch of 6-50 units, take a sample from five. In the case of batches of over 50 units, sample 10%, rounding up the number of units to the nearest multiple often. For example, a batch of 51 units would be sampled as for 60, i e. take samples from six packages.

After opening, inspect the contents of the units selected for sampling for:

-organoleptic characteristics (color, texture and odour);

-presentation of the material (raw, cut, crushed, compressed);

-the presence of admixtures, foreign matter (sand, glass, particles, dirt), mould, or signs of decay,

-the presence of insects;

-the presence of packaging material originating from poor or degraded containers.

From each container or package selected, take three original samples, taking care to avoidfragmentation. Samples should be taken from the top, middle and bottom of the container. In the case of sacks and packages, the three samples should be taken by hand, the first from a depth of not less than 10 cm from the top and the second and third from the middle and bottom after cutting into the side of the package. Samples of seeds should be with drawn with a grain probe. Material in boxes should first be sampled from the upper layer; then approximately half of the contents should be removed and a second sample taken. Finally after further removal of the material, another sample should be taken from the bottom. Samples should be as uniform as possible in mass. The three original samples should then be combined into a **pooled sample**which should be mixed carefully.

The **average sample**is obtained by quartering. Form the pooled sample, adequately mixed, into an even and square-shaped heap, and divide it diagonally into four equal parts. Take two diagonally opposite parts and mix carefully. Repeat the process as necessary until the required quantity, to within ±10%, is obtained (100-200 g for flowers and up to 10 kg for certain roots).Any remaining material should be returned to the batch.

Using the same quartering procedure, divide the average sample into four **final samples**, taking care that each portion is a representative of the bulk material. The final samples are tested for the following characteristics:

- degree of fragmentation (sieve test);

- identity and level of impurities;

- moisture and ash content;

- level of active ingredients, where possible. A portion of each final sample should be retained to serve as reference material, which may be used for re-test purposes, if necessary.

From each wholesale container (boxes, cartons, etc.) selected for sampling, take at random consumer packages. From small batches (1-5 boxes), take ten consumer packages. Prepare **pooled sample**by mixing the contents of the settled consumer packages and proceed as described above to obtain the **final sample.**

**Identification methods for new medicinal plants**

There are about 300,000 species of plants on Earth. There are at least 75 000 plant species in Eurasia. More than 6000 species of plants are found in the Caucasus. There are more than 4100 plant species in the territory of Azerbaijan. Significant wealth of domestic flora is not used enough. Hundreds of thousands tons of wild medicinal plants are not collected and died in an environmentally pure environment annually.

The development of more effective plant-originated drugs is important and actual. Pharmacognosy has a major role, since medicinal raw material and plant-originated preparations make up a significant portion of medicinal preparations. As a result of intensive study of new medicinal plants, the nomenclature of plants used in scientific domestic medicine has changed dramatically.

There are several identification techniques for new medicinal plants:

1. Learning from the experience of folk and traditional medicine. It is known that almost all plants used in modern scientific medicine have been borrowed from folk medicine. Folk medicine can influence the effectiveness of promising plants research for scientific medicine.

The early stages of the study of folk medicine are:

а)  carrying out special expeditions to collect information about local plants by acquisition of samples and population survey.

б) organization of correspondent network

Firstly, the correctness of the main medical indications for the measured subject should be tested.

If primary pharmacological (or biological) research confirms the veracity of information, then it would be appropriate to study: pharmacognostic (firstly phytochemical); technological (isolation of individual substances or producing sum preparations) and finally clinical.

2. More in-depth consideration of plants used in folk medicine. More information is obtained about chemical composition of plants by these methods. For example, Rosmarinus officinalis, Chelidonium majus, Lemon balm, blackcurrant and etc. were included in most pharmacopeois at different times, then they were excluded. In recent years, most of these plants have been entered into the register of pharmaceutical products.

3. Phylogenetic method. It has been noted that botanically related plants can have a similar chemical composition and possess similar pharmacological activity. Knowledge of these biological patterns makes the search for new medicinal plants very effective. Scientists devote excessive time to the study of the relationship between systematic position of plant and its chemical property.

4. Sieve method. There is a large-scale phytochemical analysis for main biologically active substances of plants in certain region. At the same time, it is envisaged that among the "plants passed through the analytical sieve" there are some promising plants containing alkaloids, cardiac glycosides, saponins, essential oils, lignans, tannins and other biologically active substances. Sieve method was popular in the search of medicinal plants, that’s why many expeditions were organized.

Simplified methods of quantitative determination of biologically active substances have been developed for carrying out field analysis. Sieve method played a positive role in a certain stage of science development about medicinal plants. Sieve method is laborious and empirical.

**Standardization of medicinal plant materials. Normative documents.**

Standardization is a set of standards for the quality of material, products, testing methods and etc. established by government and compulsory for producers and consumers. Mandatory rules and requirements for medicinal plant material are described in various standards, collectively called normative documents.

Modern types of normative documents for quality control of medicinal plant materials are subdivided into the following categories: 1) State standards (GOST); 2)pharmacopoeia articles (PhA); 3) [manufacturer's monograph](https://rus.proz.com/kudoz/russian_to_english/medical:_pharmaceuticals/1523574-%F0%A4%F0%A1%F0%9F.html#3538744).

State standards regulate the quality and technical requirements, testing methods and shelf life of a medicinal plant material. State standards are developed for multi-tonnage material, used in various fields of national economy, for import and export materials.

Along with state standards, methodical GOSTs are present for certain species of medicinal material, that determine the testing guidelines, sampling methods for analysis, identity and purity.

PhA is the type of ND which establishes the requirements to the MRM of  serial production, allowed for medical use according  bodies and included in State Register. PhA are industry standards and approved for 5 years.

GOSTs, PhA after approval are registered under certain number.

Manufacturer’s monograph is prepared by manufacturers and it is their property. Manufacturer’s monograph is based on PhA, but they can differ by some insignificant but noteworthy features (packaging, labeling and oth.).

Normative documents should provide the quality improvement of a medicinal plant material, be continually refined on the basis of scientific and technological achievements, be reviewed on the basis of the needs of health care and etc., that use the medicinal plant material. PhA for medicinal material is widely used in the practice of medicine and included into State Pharmacopoeia. For example, phA for 83 species of material are included in StPh XI.

In addition to these standards, industry standards, enterprise’s standards and technical conditions are used in the production.

**Qualtiy control for medicinal plant material**

The quality assurance of medicinal plant material depends upon mostly on the correct organization of control, validity and effectiveness, requirements indicated in normative documents and methods of analysis.

State system of quality control for medical preparations includes research, testing, production and use of preparations.

The system of quality control for medicinal plant material has 3 levels:

• commodity analysis in drug store (pharmacy)

• analysis: full compliance with requirements of normative documents in pharmacy;

•analysis: compliance with requirements of normative documents in pharmaceutical factories and industries.

All medicinal plant material from suppliers are subjected to  this control. Commodity research analysis is to determine the identity of a medicinal plant material. The results are recorded in a journal.

**Reception of a medicinal plant material, storage and sampling methods for analysis in warehouses (bases) and industries.**

Reception, storage and quality control of a medicinal plant material and preparations of plant origin in central pharmacy warehouses are carried out according the following rules.

All plant material from procurement is subjected to the commodity research analysis, the medicinal plant material from private procurements- full compliance with the requirements of normative documents.

When the medical preparations of plant origin are sent to other pharmacy warehouses (bases), each batch is accompanied by a certified copy of the analysis protocol, which proves its quality. When medicinal preparations are entered other warehouses, they are not subjected to repeated analysis, except the quality  is in question.

Medicinal plant material and preparations containing cardiac glycosides from procurements and appropriate companies along with main terms of reception rules the following charactersitcs should be tested:

a) biological activity of each packing, indicated on the label (valor) and the date of collection for medicinal plant material

At the same time the presence of this information should be checked in the accompanying documents.

If this information is missing, pharmacy warehouses should urgently require it from supplier.

b) determine the compliance of biological activity of medicinal plant material and preparations with the requirements of the State Pharmacopoeia (technical conditions, temporary technical specifications and other regulatory technical document)

Medicinal plant materials and preparations that do not comply with the requirements of the normative-technical document should be returned to the organization, and the medicinal plant material with high biological activity can be admitted to the pharmacy and production of galenical preparations. However, the unit of activity of 1 g material, the weight of material equivalent by acitivity to 1 g standard material should be indicated on the label of the medicinal plant material.

Medicinal material with low biological activity, in exceptional cases can be admitted to warehouses for sending to galenical factories (this kind of material is not admitted to pharmacy).

Average sample should be selected according to the requirements of normative document on this material, and if these requirements are not present- according the State Pharmacopoeia "Average sample”.

Average sample is packed, labeled, according to Pharmacopoeia requirements- the raw material, batch number, lot, date of sampling, and  name of a person selected the sample and sent for analysis.

Average sample of raw materials for analysis is registered in the journal and monitored according to all quality indicators by methods established in the normative document for this material. If the quality of material meets the requirements of normative document, technical control department or analytical laboratory issues 3 copies of passport. One copy – as the basis for release of material, is stored in the warehouse for 1 year, the second - to the consumer, the third – to technical control department or analytical laboratory.

The number of the certificate should conform with the serial number of the analysis in the journal. The results of the analysis are added to the card. Each card reflects the results of analyzes for all bathces of materials for the current year.

Head of the department technical control or analytical laboratory write a report of expiry date of preparation based on the results of the analysis.

Analytical passports, journals and cards are stored for 3 years, and workbooks are stored for one year.

Number of analysis on the leaflet of material and stamp of the technical control department with the word "useful" is placed on.

When the material does not comply with the requirements of the normative-technical document, the technical control department sends the analytical passport to the supply, the raw material is isolated and the dimensions are taken according to the article "The rules for dispatching products for technical production purposes".

Medicinal material and preparation in pharmacy warehouses should be stored in a dry place protected from sunlight, in accordance with the requirements of the State Pharmacopoeia, Technical Conditions and Temporary Technical Conditions.

Medicinal plant material should be stored at the temperature not more than 20 ° C and humidity not more than 30-40%, and liquid medical preparations - not more than 12-15 ° C and humidity –not more than 60%.

Biological activity of medicinal plant material and preparations containing cardiac glycosides should be tested periodically on the basis of shelf life and re-inspection time indicated in the analytical-normative documents. Without this inspection, they should not be admitted to pharmacy.

If the biological activity is decreased in medicinal plant material and preparations containing cardiac glycosides, preparations are excluded and destroyed, and material can be used in the production of galenical preparations. Biological activity should be tested if the appearance of the medicinal plant material and preparations is changed before the expiry date. Their use is determined depending on this result.

When the reanalysed medicinal plant material and preparations are admitted, pharmacy storekeeper should register this information in the accompanying documents.

**The reception of medicinal plant material and Прием лекарственного растительного сырья и отбор средней пробы**

Medicinal plant material is entered the drug stores (pharmacy) and bases in big packaging or pre-packages, in briqueettes and oth. The identity, purity, quality and suitability of material are determined and after the positive results it is admitted to reception.

Reception of material is carried out according to State standard 24027.0-80 and the following scheme:

1) Visual inspection of packaging

2) Selection of certain packages for sampling

1. Determination of uniformity in selected packages and detection of paucity in them
2. Average sample

Inspect each container or packaging unit for conformity with the requirement of normative doucments regarding packaging and labelling. Check the condition of the package and not any defects.

When a batch consists of five containers or packgaing units, take a sample from each one, from a batch of 6-50 units, take a sample from five, in case of batches of over 50 units, sample 10% routing up the number of units to the nearest multiple if ten.

After opening inspect the contents of the units selected for sampling for uniformaty, colour, odour.

If the poisonous plants, stone, sand, paper, mold and rot, a persistent foreign smell that doesn’t disappear during air exchange, loss of specific odour are present in plant material, then it is not accetaple. If these deficiencies are not present, the material is taken from the top, middle and bottom. Average sample is selected from initial sample. The initial sample is spread out on a glass in a square pattern and levelled. The square is divided into 4 triangles by 2 diagonals. Two of the opposing triangles are remove, the remaining triangles are joined. This operation is repeated until the amount of raw material in the 2 opposing triangles corresponds to the weight of average sample in the table. The weight of average sample is established for each certain material: for roots and rhizomes – 400 g, leaves – 400 g, blossoms- 150-200 g, chopped herb – 200 g.

Average sample is divided into several small samples and identity, purity, quality are determined.

Commodity analysis

 Commodity research analysis of medicinal plant material determines purity.  Commodity research analysis consists of 3 stages: reception of raw material, sampling and analysis of 3 analytical samples. Commodity analysis of medicinal plant material is carried out according to the State Pharmacopoiea XI.

The reception of medicinal plant material.

 The reception of medicinal plant material is carried out in batches. A batch is amount of material with the weight not less than 50 kg and more than one type, uniform and issued by one document that confirms its quality. The document includes: 1) number and date of issue of document; 2) name and address of sender; 3) name of raw material; 4) batch number.; 5) weight of the batch; 6) year, month of material procurement; 7) the area of preparation (for wild medicinal plants); 8) results of trial of raw material quality; 9) normative document on raw material; 10) signature of person responsible for the raw material quality - name and title of a person selected the sample.

Inspect each container or packaging unit for conformity with pharmacopoeia monographs or other requirements regarding packaging and labeling. Check the condition of the package and note any defects that may influence the quality or stability of the contents (physical damage, moisture, etc.).

To control the quality of raw material matching with the requirements of the normative document take a sample from undamaged units in different places of the batch, indicated in the table 00.

Table . The quantity of material for determination of its quality

|  |  |
| --- | --- |
| Quantity of units | the volume of excerption |
| 1-5  6-50  over 50 | All units  5 units  10% units of packed raw material |

**The quality control of raw material in damaged units is carried out separately, opening each unit of production separately.**

*Note.* Incomplete 10 units of production are equated to 10 units (for example, if a batch of 51 units would be sampled as for 60, i.e. take samples from 6 packages).

The units of production under excerption are opened and in the units of production check the uniformity of raw material according to preparation method (whole, crushed, pressed), the colour, the odour of raw material, the presence of mold, rot, unpleasant odours, poisonous plants and impurities (stones, glass, hay, etc.). The presence of granary pests is determined by unaided eye and 5-10x magnifying glass.

If the stale, stable foreign smell, poisonous plants, impurities (poultry and rodent droppings, glass), II and III degrees of granary pest contamination are found in raw material, the batch of raw material is not accepted.

**Sampling methods for analysis**

Medicinal plant material is entered the drug stores and bases in big packaging or pre-packages, in briqueettes and oth. The identity, purity, quality and suitability of material are determined and after the positive results it is admitted to reception.

From each container or package selected, take three original samples, taking care to avoid fragmentation. Samples should be taken from the top, middle and bottom of the container. In the case of sacks and packages, the three samples should be taken by hand, the first from a depth of not less than 10 cm from the top and the second and third from the middle and bottom after cutting into the side of the package. Samples of seeds should be withdrawn with a grain probe.. Material in boxes should first be sampled from the upper layer; then approximately half of the contents should be removed and a second sample taken. Finally after further removal of material, another sample should be taken from the bottom. Samples should be as uniform as possible in mass. The three original samples should then be combined into a pooled sample which should be mixed carefully.

At the revealing of  granary pests in raw material from the combined samples by means of quartation select analytical sample weighing 500 g for small kinds of raw material and weighing 1000 g for big kinds of raw material, put them into the a tightly closing pot, mark for determining the degree of pest control.

Average sample is selected from combined sample by quartation. The raw material is placed on smooth, clean, flat surface, it is mixed, spread out on a piece of paper in thichk layer in a square pattern and levelled. The square is divided into 4 triangles by 2 diagonals.Two of the opposing triangles are remove, the remaining triangles are joined. This operation is repeated until the amount of raw material in the 2 opposing triangles corresponds to the weight of average sample in the table. Allowable deviations in the weight of average sample should not be more +/- 10%.

Table. The weight of average and analytical samples of medicinal plant raw material for commodity analysis.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Raw material | The weight of average sample, g | | | |
| Average | Analytical | | |
| № 1 | № 2 | № 3 |
| Pine buds | 350 | 200 | 25 | 100 |
| Birch buds | 150 | 50 | 25 | 25 |
| Whole leaves except the following:  Senna leaves  Leaves of bearberry and cowberry | 400  200  150 | 200  100  50 | 25  15  25 | 150  50  50 |
| Cut, thrashed leaves | 200 | 5 | 25 | 100 |
| Blossoms, except the following:  Calendula blossoms and corn silk  Elderberry blossoms  Chamomile blossoms | 300  200  75  200 | 200  100  20  50 | 25  25  15  25 | 50  50  25  100 |
| Whole herbs except the following:  Herb of origanum | 600  150 | 300  25 | 50  15 | 200  50 |
| Cut, thrashed herbs | 200 | 50 | 25 | 100 |
| Juicy fruits, except the following:  Rose hips  Fruits of pepper | 200  300  550 | 100  200  300 | 50  25  25 | 50  50  150 |
| Dried fruits and seeds except the following:  Datura inoxia seeds, thermopsis, ammi fruits and jute seeds | 300  200  150 | 200  50  10 | 25  25  25 | 50  100  100 |
| Tubers, roots and rhizomes, except the following:  Rhizome and roots of common madder, tormntil rhizome, roots and rhizomes of inula, rhizome of male fern, rheum root  Purified root of licorice unpurified root of licorice, , root of barberry | 600  400  1000  1500  2500  6000 | 300  200  600  1000  2000  5000 | 50  50  50  100  100  100 | 200  100  100  300  200  500 |
| Chopped, crushed roots and rhizomes | 250 | 100 | 25 | 100 |
| Whole bark | 600 | 400 | 50 | 100 |
| Chopped bark | 200 | 100 | 25 | 50 |

Note. The whole medicinal plant material is chopped with scissors, thoroughly mixed and then the appropriate analytical samples are isolated.

The average sample is packed into the plastic or multiwall paper bags, it is labeled. The 2d label is put inside the bag. The name of raw material, name of supplier, batch number, weight of the batch and the average sample, date of sampling, name and title of a person selected the sample are indicated on the label.

Analytical samples are selected from the average sample by quartation for the determination:

- Sample number 1 - for determining the authenticity, fragmentation and impurity;

- Sample number 2 - for determining the humidity (it is separated and packed immediately after selection of the average sample;

- Sample number 3 - for determining the content of ash and BAS.

Weighing error of analytical samples is allowed ±:

± 0,01g — weight of sample to 50 g;

± 0,1g — weight of sample from 100 to 500 г;

± 1,0 g — weight of sample from 500 to 1000 г;

± 5,0 g — weight of sample above 1000 г.

If the quality of raw material doesn’t meet all requirements of normative document, it is re-tested. The excerption is selected from unopened units of production according to the table for reanalysis. The results of reanalysis are final and applied to the whole batch.

*Note!* The presence of radionuclides should be checked before the complete pharmacognostic analysis is carried out.

Analizin nəticələri aşağıda verilmiş formada sertifikatlaşdırılır.

Certificate of analysis

Chamomile blossoms .

. (material name)

Batch number\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_Reception date

Quantity in batch (kg, pieces and oth.).

Supplier

(name of organization)

Sampling date Sample is taken by

Surname

Results of external inspection Analysis is made

(name of analytical normative document

|  |  |  |  |
| --- | --- | --- | --- |
| №  n/n | indicators | Indicators in normative documents | Actual indicators |
| 1 | external characteristics | StPh XI, ed.2 p. 7 |  |
| 2 | Microscopy | StPh XI, ed.2 p. 7 |  |
| 3 | Humidity | Not more 14 % |  |
| 4 | Essential oil | Not more 0,3 % |  |
| 5 | Total ash | Not more 12 % |  |
| 6 | Ash insoluble in 10% hydrochloric acid | Not more 40 % |  |
| 7 | Leaves, stems, anthodiums with Листья, стебли, корзинки с остатками цветоносов | Not more 9 % |  |
| 8 | Blackened and brown anthodium | Not more 5 % |  |
| 9 | Organic impurities | Not more 3 % |  |
| 10 | Mineral impurities | Not more 0,3 % |  |
| 11 | Packing and marking | Should be complied with the reuqirements of PhA 42U-52-41-95 |  |

Analysis is made by

(date, position, surname) (signature)

Results of QC

Head of QCD\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

(signature) (encoding) (date)

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QCD - Quality control department

YOXLAMAQ0000000000000000000000000000000000000000000000

Certificate of analysis

Chamomile blossoms

Batch number-----------------Date of reception------------------------

Quantity (kg, pieces and etc.) batch number

Procurement officer--------------------------------------------

Date of sampling Sample was taken:

Results of external inspection Analysis was made -------------------

The determination of moisture content of medicinal plant material.

Humidity - the loss of raw material weight at the expense of moisture and volatile substances.

Method. The amount of the raw material indicated in individual monograph is placed in a weighing bottle, preliminary dried under the conditions described for the raw material. Raw material is dried to constant weight or during the time indicated in individual monograph, by the following methods:

Sample number 2 is grinded to a particle size of about 10 mm, 2 weighed amounts of 3-5 g are taken, accurately weighed to within 0.01 g. Each weighed amount is placed in tray drier and weighed and dried in an oven at 100-105 C. The drying time is counted from the moment when the temperature in an oven re-stabilises at 105°C. First weighing of leaves, herbs and flowers is carried out in 2 hours, roots, rhizomes, barks, fruits, seeds and other types of raw material – in 3 hours.

The drying process is carried out to constant weight. Constant weight is reached when two consecutive weighings after drying for 30 minutes and cooling for 30 minutes in a desiccator, show not more than 0.01 g difference. The determination of the loss in mass on drying for recalculating the amount of active substances and ash in absolutely dry raw material is carried out in 1-2 g weighed amounts taken from sample number 3 for determining the content of ash and BAS, as described above, with not more than 0.0005 g difference

The moisture content % is calculated by the formula:

Where *m*— weight of raw material before drying, g; *m*1 —weight of raw material after drying, g.

The result is an arithmetic mean of two parallel determinations, weighed at 0,1% precision. The allowable difference in 2 parallel determinations should not be more 0,5%.

Determination of fragmentation.

Method. The sample is placed on sieve indicated in the relevant normative document for this medicinal material, and sieved carefully by smooth rotational movements, without additional grinding. Sieving of grinded parts is considered to be complete if the amount of raw material passing sieve in one minute is less than 1% of the raw material retained on that sieve.

The particles of whole raw material passing sieve are weighed and calculated their percent to the weight of sample.

2 sieves are taken for crushed, chopped and oth. raw material. The sample of raw material is placed on the top sieve and sieved.  Then, the raw materials retained on the top sieve and passed through the sieve are weighed separately. The percentage of particles that not passed through the upper sieve and particle content that passed through lower sieve to the weight of the sample are calculated. Weighing is carried out with an error ±0,1 g if the weight of sample is above 100 g and ±0,05 g if the weight of sample is 100 g and less.

Permissible limits of crushed particle content are indicated in relevant normative document.

Determination of impurity content.

Impurities are the foreign parts of plants and components that may be present in raw material due to the preparation, drying and application. During the collection non-standard parts of this plant or other plants growing nearby can be in the raw material. The raw material is grinded during drying and packaging, soil, sand, straw can be in raw material. Standards permit the certain percent of impurities for each type of raw material.

The impurities in medicinal raw material are divided into organic and mineral, permissible and impermissible.

*Organic impurities are*: *1)* parts of the same plant that do not conform to the name of the material specified in the analytical normative document; the number of them varies and for each type of raw materials is given in the standards separately (usually 2-5% is permitted).  2) impurities of other plants: rods, hay, straw ( average 5% is permitted); 3) parts that lost their color (brown, blackened, etc.) (1-6% is permitted);4) the crushed parts formed during drying and packing (2-5% is permitted, for matricaria -20%).)

Mineral impurities are often found due to the collection and treatment (sand, soil, stones), rarely – packaging. 0,5-2% of these impurities are permitted for various raw material.

Impermissible impurities are: 1) poisonous plants; 2) metal objects; 3) glass; 4) rodent and bird droppings; 5) other similar plants.

Permissible impurities are organic and mineral impurities, their content in the raw material in quantities not exceeding those established in the ND norm.

The presence of foreign impurities reduces the purity and quality of medicinal raw material and the quality of finished medicinal products.

Method. The retained part of analytical probe No. 1 after screening of crushed particles (for whole raw material) or descending from the upper and lower sieves (for cut, crushed and other crushed raw materials) is placed on a flat clean surface and the impurities indicated in the normative technical documents on medicinal plant raw materials are isolated by spatula or tweezers. The impurities are: - parts of raw material, which lost the colour, typical for this kind;

- other parts of the producing  raw material that are not the raw material;-

-  organic impurities (parts of the other non-poisonous plants)

- mineral impurities (sand, soil and small stones).

At the same time, attention is paid to the presence of granary pests.

Each type of impurity is weighed separately with the error ±0,1 g if the sample weight is more than 100 g and with the error ±0,05 g if the sample weight is 100 g and less.

The impurity content % is calculated by the formula

where *m*1 — weight of impurity , g;

*m*2 — sample weight of raw material , g.

Determination the degree of contamination by granary pests.

Detection of granary pests in material

The special isolated analytical sample is used.

Method. Analytical sample of plant raw material is sieved through a sieve with a size of hole of 0,5 mm. The presence of mites are checked in the raw material passed thorugh a sieve, the presence of moths, grinder, weevil and their larvae, live and dead insects are checked in the raw material remained in a sieve. The number of ticks is counted using a magnifying glass, the number of moths, its larvae, pupae and other pests - with the naked eye and using a magnifying glass. The number of found pests and their larvae is recounted for 1 kg of raw material and the degree of its contamination is established.

If there are no more 20 mites in 1 kg of raw material (*Tyroglyphus farinae*, *Glyciphagus destructor*, *Сheyletus eruditus, carpoglyphus lactis* and oth) the contamination of raw material is referred to I degree, the presence of more than 20 mites freely moving along the surface of the raw material and not forming continuous masses - to the second degree, if there are many mites, they form continuous felt masses, their movement is difficult - to the third degree.

If there are no more 5 wolf moth (Tinea granella) and its larvae, drugstore beetle (*Sidotrepa panicea*), and oth. in 1 kg of raw material,. the contamination of material is referred to I degree, 6-10 pests – to II degree, more than 10 pests – to III degree.

If the pests are found in medicinal plant material, it is subjected to disinfestation, after it is sieved through a sieve with a size of hole of 0,5 mm ( contaminated with ticks), or with a hole 3 mm in diameter (contaminated with other pests).

After the raw material is treated, it is used depending on the degree of contamination. At 1 degree of contamination the raw material can be admitted to medical use, at 2 degree of contamination and in exceptional cases at 3 degree of contamination the raw material can be used for the treatment in order to obtain individual substances.

The determination of the ash in medicinal raw material.

Ash is non-combustible inorganic residue obtained after burning and calcination of raw material. There are the total ash and the ash insoluble in 10 % solution of hydrochloric acid. The total ash  is the amount of mineral substances, specific for the plant, and extraneous mineral impurities (sand, soil), caught into the raw material while collecting and drying.

Ash insoluble in 10% hydrochloric acid  is a fireproof residue obtained after processing the total ash with hydrochloric acid and mainly consisting of silica. Higher content of acid insoluble ash indicates the significant amount of mineral impurities in medicinal plant material.

The determination of ash ( Method (SPh ХI, edit. 2, p. 24). Sample number 3 is crushed and sieved through a sieve with a size of the hole of 2 mm. About 5,0 g (accurately weigh) of raw material is placed in a precalcined to constant weight porcelain, quartz or platinum crucible

A plant material is carefully fused in the crucible over a weak flame of the burner or on an electric plate on which an asbestos mesh is placed.

After complete carbonization, the crucible is transferred to a muffle furnace to fuse the coal and calcine the residue completely.

Calcination is carried out at a red heat (350-500 ° C) to constant weight, avoiding ash fusion and sintering it with the walls of the crucible. At the end of the calcination thr crucibles are cooled during 2 hours, then they are placed into dessicator, anhydrous calcium chloride is present at the bottom of desiccator, then they are cooled and wieghed..

The weight is considered to be constant when the difference between two weightings is less than 0.0005 g.

If it is impossible to burn the coal completely, then a residue is cooled, wetted by water or saturated ammonium nitrate solution, the liquid is evaporated in a water bath and the residue is calcined. If it is necessary the operation is repeated several times.

Acid-insoluble ash

Method. To the crucible containing the total ash, add 15 ml of 10% hydrochloric acid (~1,050 g/cm3), cover with a watch-glass and boil gently for 10 minutes. Rinse the watch-glass with 5 ml of hot water and add this liquid to the crucible. Collect the insoluble matter on an ashless filter-paper and wash with hot water until the filtrate is neutral. Transfer the filter-paper containing the insoluble matter to the original crucible, dry on a hotplate and ignite to constant weight. Allow the residue to cool in a suitable desiccator, then weigh without delay.

2 parallel determinations are carried out

The content of total ash % in air-dried material:

where *m*1 — mass of ash, г;*m*— weight of material, g;

*W*— weight loss due to drying, %

The content of acid-insoluble ash in air-dried material:

where *m*2 — weight of ash, g;

*m*3 — weight of filter ash (if its ash is not more than 0,002 g);*m*— weight of material, g;

*W*— weight loss due to drying, %

The test result is the arithmetic mean of 2 parallel determinations. Calculation is carried out to 0,01% for the raw material with not more than 5% ash content, to 0,1% - for the raw material with more than 5% ash content, the permissible differences between them should not exceed 0.1% for raw materials with 5% ash content, and 0,5% - for raw material with more than 5% ash content.

Determining the amount of extractives.

Extractive values of crude drugs are useful for their evaluation, when the quantative determination is absent in analytical normative document.

Extractives of medicinal plant material are complex of organic and inorganic substances, that are extracted with the solvent from a given amount of medicinal plant material. Their content is determined gravimetrically as a residue remaining after drying.

The solvent for determination of extractive values is indicated in analytical normative document for certain material. It is usually a solvent that is used in the production of tincture or extract from the medicinal plant material.

Method. About 1 g of crushed material (accurately weighed) with particle size 1 mm is placed in a round-bottom flask of 200-250 ml and 50 ml of solvent is added (indicated in the relevant analytical normative document for medicinal medicinal material). Stopper the flask and weighed (the error ±0,01 g) and left for 1 hour. Then the flask is conneted to a reflux condenser, heated, keeping weak boiling during 2 hours. After cooling, stopper the flask and weigh and replenish the lost weight with the solvent. The flask is shaken frequently and filtered through filter paper in a dry 150-200 ml of flask. 25 ml of filtrate is placed in a predried at a temperature of 100-105 С accurately weighed porcelain cup with a diameter of 7-9 cm and evaporated to dryness in a water bath. Cup of dried residue in an oven at a temperature 100-105° С to constant weight, then it is cooled for 30 min in a desiccator over calcium chloride and is weighed.

The content of extractives % is calculated by the following formula (in terms of air-dried material):

where *m*— the weight of dry residue, g;

*m*1 — weight of material, g;

*W*— weight loss due to drying %.