

## ROMANIAN PHARMACOPOEIA FROM THE FIRST TO THE LAST EDITION

Valentina SOROCEANU  
UMF “Carol Davila” Bucharest

The development of the **First Edition of Romanian Pharmacopoeia** was conducted by a group of professionals led by Carol Davila. This group consisted of 12 physicians and 6 pharmacists.

At the suggestion of Davila, the Pharmaceutical Council consulted several pharmacists in the country as well as in Bucharest with regards to establishing the specific pathology in various parts of the country, and with the purpose of introducing various original prescription formulas in this first pharmacopoeia.

Hence, on December the 5<sup>th</sup> 1862, the Medical Council approves the first edition of the Romanian Pharmacopoeia which became applicable starting with January 1863. The volume represented a valuable work which corresponded entirely to the scientific requirements of that time. Comprising 790 pages divided into three parts, the edition was written in two columns, both for Romanian and Latin language.

### First Edition of Romanian Pharmacopoeia



The pharmacopoeia was published in 1862 in Bucharest, under the reign of Alexandru Ioan I, as follows:

**‘by the grace of God and the will of the People’ (Sovereign of the United Principalities)**

**Typography of the Otelu Bossel National Journal, Nr. 34, 1862**

**Bucharest, January the 9<sup>th</sup> 1863**

**‘to all present and to all in the future good health’**

The first part, *Materia pharmaceutica*, comprised 301 monographs, out of which 207 were herbal drugs, 23 were of animal origin, 46 inorganic substances and 15 organic compounds. More than half of the vegetal products came from the country, many of them still used today with therapeutic purposes, for example: *Matricaria chamomilia*, *Hypericum perforatum*, *Artemisia absinthium*, *Arnica Montana*, *Chelidonium majus* etc. Some of the animal origin drugs include: *Jecoris aselli*, *Cetaceum*, *Cera*, *Cantharide*, *Fel bovinum*.etc.

The inorganic substances category only included substances which could be purchased commercially: *Sulfas magnesiae*, *Argentum foliatum*, *Acidum chlorhidricum*. Among the organic substances comprised in the pharmacopoeia, we mention camphor oil, indigo, vinegar, creosote and sodium soap.

*Preparata Pharmaceutica*, the second part of the volume, contains 547 monographs of galenic products and pharmaceutical formulations as well as organic and inorganic substances which were developed in pharmacy (boric acid from borax, barium chloride from barium sulphate and so on).

The last part of the Romanian Pharmacopoeia, *Reagentia et Tabulae Variae*, contains 52 tables and a list of foreign names and their popular synonyms of some of the most important drugs, as well as the instructions for the preparation of popular drugs.

**Eg.:**

*Unguentum ophtalmicum Janini*

White precipitate of mercury 1

Prepared Tutia

Armenian Bulu / aa 2

Lard 4

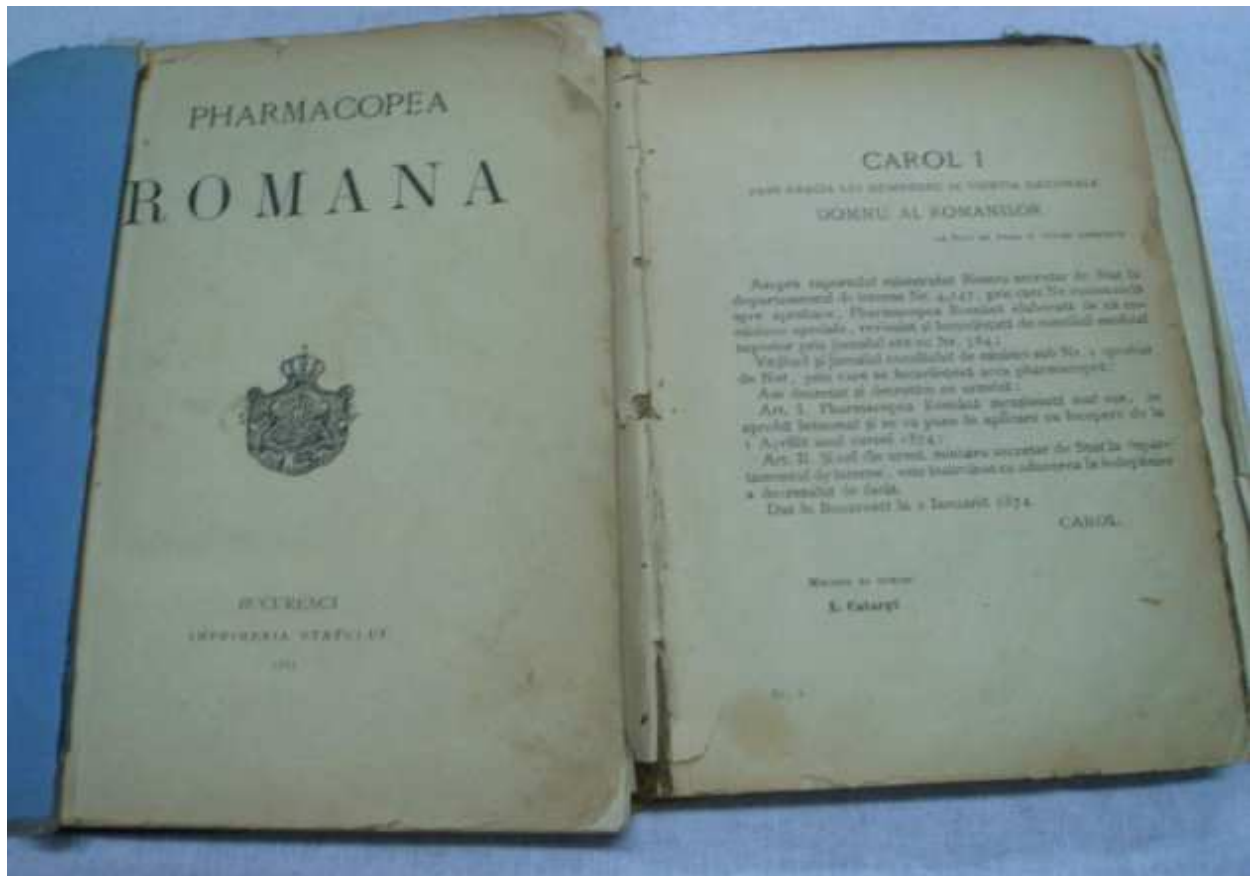
**Tabula I.** - Antidotes and some formulas for annihilating poisons.

**Tabula II.** - Poisonous drugs and their conservation.

**Tabula III.** - Highly active drugs.

The development of the first edition of the Romanian Pharmacopoeia required the elaboration of the first autochthonous fee, ‘Drug fee for the United Principalities’, published in 1864.

## Second Edition of Romanian Pharmacopoeia



In 1874, together with the approval of the first health law in Romania, appears the **Second Edition of Romanian Pharmacopoeia**, printed by the State Printing Office in Bucharest. This paper however has much smaller dimensions than the first one. Containing 160 pages only, this edition is written only in Romanian and it comprises 13 tables and one index. Compared to the first edition, the second pharmacopoeia brings some changes, so the narcotic aqueous extracts from the first volume are replaced with alcoholic extracts for better preservation. Another novelty is that this new edition establishes the part of the plant with the richest content in active principles, for example the omag tubers or the mandrake root, as opposed to the aerial part of the plant, which was provided previously. In general, this second edition decreases the concentration of dyes and inserts the decimal ratio for better dosing and easier calculation of quantities.

This edition is written in Romanian only, comprises a total of 522 monographs, out of which – 316 pharmaceutical substances monographs and 206 pharmaceutical formulas. Analyzing the origin of these substances, one can notice that the vegetable substances are predominant (~57%), 120 are of chemical (~38%) and animal origin (~5%).

### Third Edition of Romanian Pharmacopoeia



Two decades afterwards, in **1893**, the **Third Edition of Romanian Pharmacopoeia** appears, elaborated by a special Commission appointed by the Ministry of Interior.

Printed at the State Printing Office in Bucharest and approved by the Superior Health Council in June 12, 1892, this edition is implemented by decree starting with June 22, 1892.

This volume is much more complete than the previous one, containing 476 pages divided into three parts.

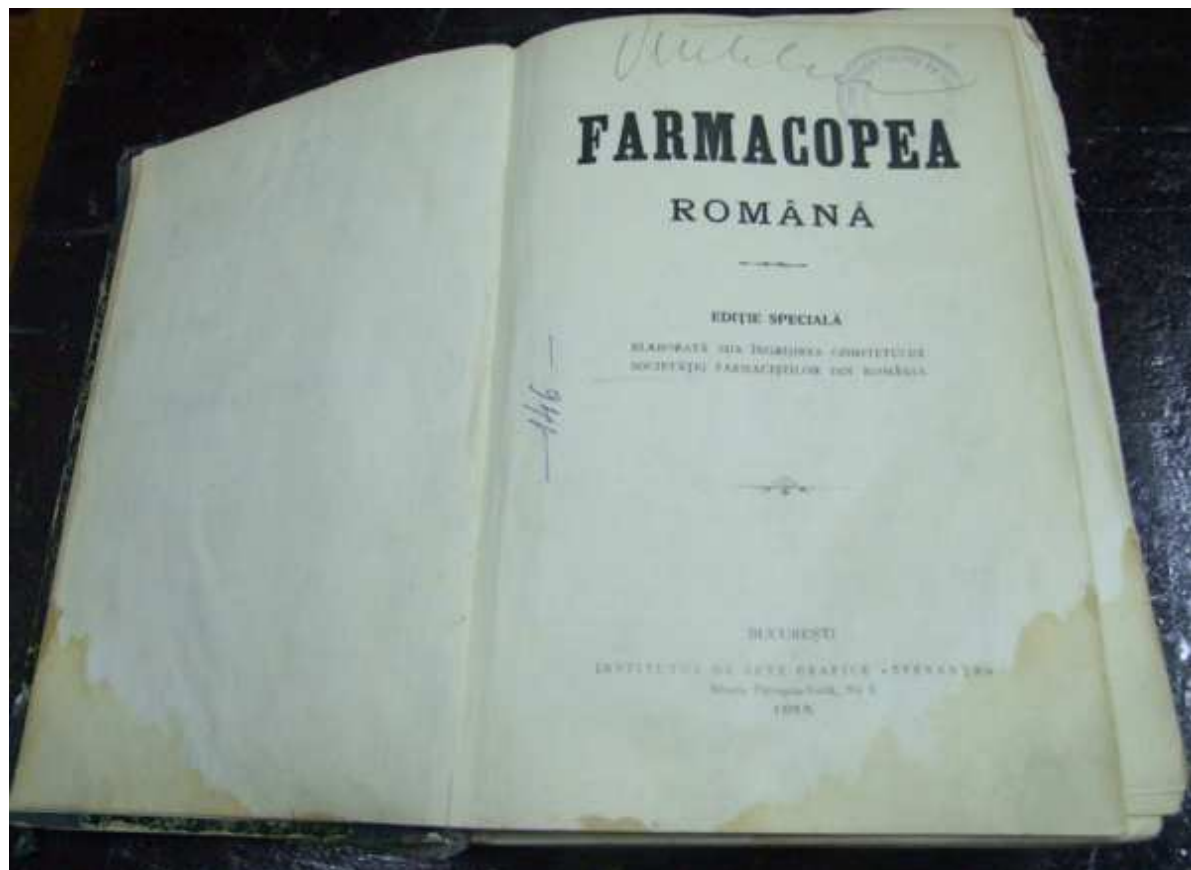
The first and the second part include monographs of medical substances (395) and of galenic preparations (301).

The first part of this edition is divided into two sections, the first one with reference to plant and animal products developed by professors D. Gecescu and N. Măldărăscu, and the second section, elaborated by professors C.I. Istrati and N. Măldărăscu, deals with chemical substances .

The making of the monographs implies the introduction of the atomic formula and molecular weight and, for the first time, the insertion of certain microscopic characteristics of various herbal drugs (Amilum, Licopodium). Chemicals also include a series of active principles of vegetable products: atropine, caffeine, digitalina amorphous, aconitine, quinine, ergotinine, and, for some of these, the instructions of preparation as well. Other substances of chemical origin are introduced: phenacetin, acetanilide, antipyrine, as well as a number of 11 animal products (2,78%). This edition of the Romanian Pharmacopoeia first introduces veterinary preparations (part III).

We owe the appearance of the **Romanian Pharmacopoeia, Special Edition 1915** to pharmacist Constantin Kollo (1874-1954), who, after many efforts, succeeded in elaborating this paper which he wanted to embody a ‘mirror of his times’ (it has been 22 years since the 3<sup>rd</sup> edition), as an update to the current state of knowledge was required. ‘Elaborated under the care of the Romanian Pharmacists Society Committee and edited by Speranta Institute of Graphic Arts in 1915’, the paper consists of 709 pages and a number of 813 monographs presented in alphabetical order in Latin, followed by the Romanian equivalents.

### **Romanian Pharmacopoeia, Special Edition**



The development of this edition had as documentation sources the European pharmacopoeia existent at that time, the heroic drugs list elaborated by the International Pharmacopoeia Commission (Bruxelles – 1906) and the American Pharmacopoeia. The heroic drugs in the 1915 edition are marked PI (Pharmacopoeia Internationalis).

The paper begins with ‘General rules’, it contains a set of 26 regulations, numbered in Arab, and it refers to various aspects of pharmaceutical practice. For example:

- The phrase ‘just weighed’ (‘to the 4<sup>th</sup> decimal’) is being explained.
- The word ‘water’ or ‘aqua’ refers only to distilled water.
- If the concentration of an acid is not established, then it is understood that the acid is considered in concentrated form.
- Rules of determining the melting point.
- Iodine parameter.

- The degree of divisibility of the drugs is expressed in Roman numerals in parentheses, placed immediately after the name of the drug (pharmaceutical screens I-VIII).
- The microscopic examination of the drugs powders must be done in a drop of water, unless stated otherwise.

According to the 'Pharmacopoeia Internationalis' decisions, the names of the acids containing Oxygen in their molecule are updated with the Latin ending '*icum*', eg.: Acidum sulfuricum, Acidum nitricum. The same ending is used for the salts of these acids, eg.: Natrium nitricum, Natrium hydrochloricum.

The novelties contained in this edition mention vials in a separated chapter, which describes the processes of vial filling, checking and sterilization. Another novelty is the mentioning of some new ways of sterilizing the substances used for hypodermics and of the molecular weights calculated based on the last atomic weight, as it was established by the International Special Commission in 1913.

It is noticed that, depending on the provenance (origin) of the medical substances, the chemical ones occupy over half of the total (59%), the vegetable ones around 36%, while the animal origin substances 23%.

The lead author recommends pharmacists to use this edition in their professional practice. Even though this issue was not formalized, it has not affected the quality and real value of the work.

## Fourth Edition of Romanian Pharmacopoeia



Due to the historical events in the early twentieth century, as well as to the process of completion of the formation of the Romanian National State, it has been 33 years since the 3<sup>rd</sup> edition of the Romanian Pharmacopoeia, and the implementation of a new edition was imposed, a thing which materialized in 1926, with the publication of **the Fourth Edition of Romanian Pharmacopoeia**.

The volume came into being thanks to the initiative of pharmacist Alexandru Iteanu, who, at that time, also had the function of president of the General Association of Pharmacists in Romania. Among the people contributing to the preparation of this fourth edition, we mention pharmacists Emil Belcot, Gheorghe Hotăranu, Alexandru Komornichi and others (3). Compared to the third edition, the fourth edition introduces several new monographs of medicinal substances, drugs and preparations such as: Barium sulfuricum, Sirupus Kali sulfoguaiacolicus, Species diureticae (radix ononidis, Pertoselini radix, radix Liquiritiae fructus Juniperi in equal parts).

Additionally, this edition officializes organic substances of synthesis that enrich the therapeutic arsenal. From a structural point of view, PR:V consists of two parts. The first part contains descriptions of both substances and medicinal forms, arranged in alphabetical order. Out of 699 monographs, 438 are substances.

The second part of the edition consists of tables, boards containing raw materials in alphabetic order (Index alphabeticus) and a table containing the Romanian names of substances in the pharmacopoeia. The paper is approved by decree No. 1443, signed by King Ferdinand I on the 27<sup>th</sup> of March 1926.

## Fifth Edition of Romanian Pharmacopoeia



**The Fifth Edition of Romanian Pharmacopoeia** represents the initiative of the Medicine Academy of Bucharest which, with the approval of the Ministry of Health, forms a commission under the presidency of Professor D. Danielopolu. This commission consisted of teachers from the Faculty of Pharmacy and Medicine in Bucharest, delegated of the Ministry of Health, and the president of the General Pharmacists College. The 5<sup>th</sup> edition was edited in 1943, in hard conditions, due to war.

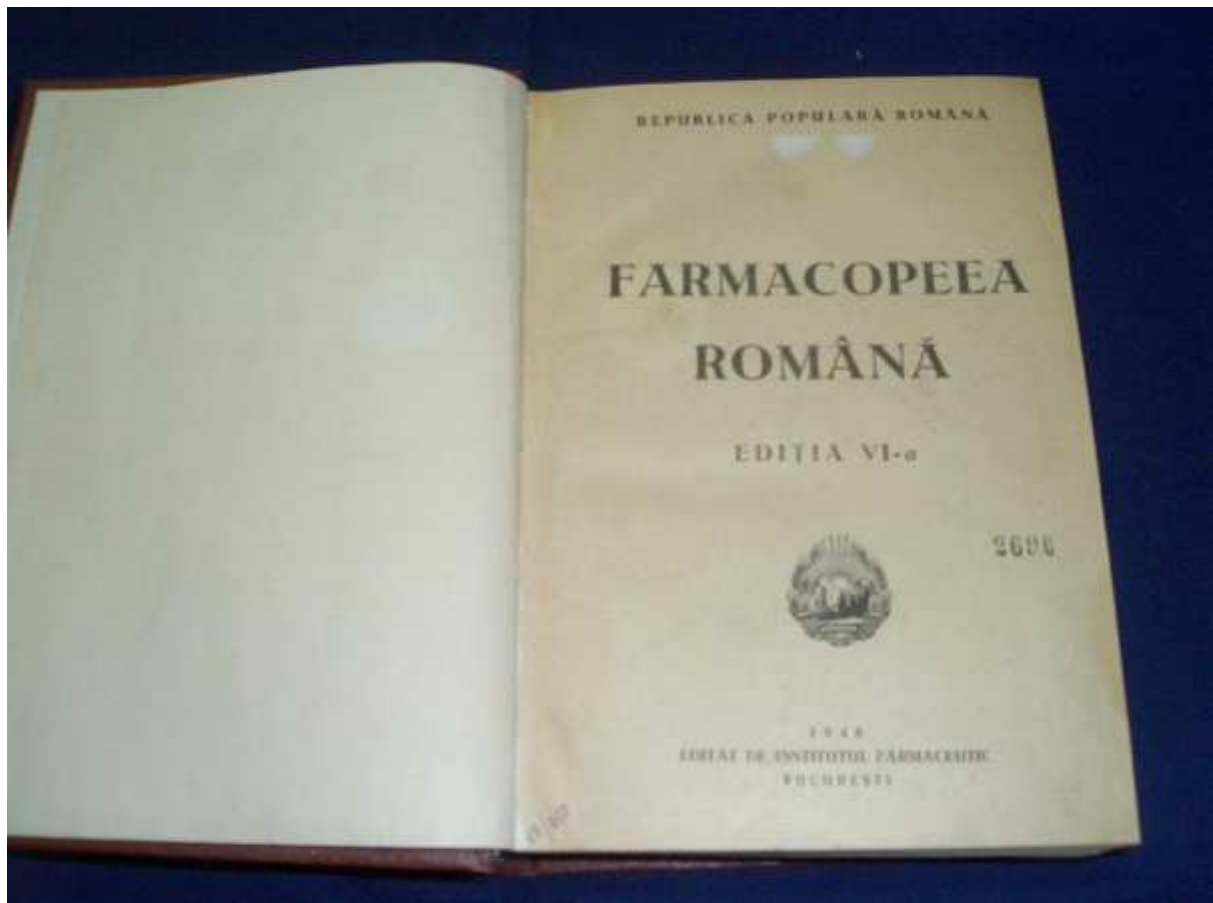
This new pharmacopoeia is structured in two parts and, in addition to the previous one, each monograph also contains identification and purity reactions. Among the particularities of this volume, we mention the introduction of verifications for hormone and pharmaceutical eradicators in glands of internal secretion, using pharmacodynamic methods, because they could not be assayed using physicochemical methods.

Also, the new edition introduces quantitative dosages for drugs, medical substances and preparations for example: water in *Adeps siullus*, and in *Ammonium sulfoichtyoilicum*, calcium in *Calcium lacticum*. With a total of 677 monographs, out of which 429 substances and 248 galenic products, we notice once more that substances of chemical origin are more than half of the total (59%), while vegetable substances are around 36% and animal substances approximatively 5%.

Summarizing the 5<sup>th</sup> edition of the Romanian Pharmacopoeia, there are a couple of features that can be distinguished: toxic dose specification, due to our country's accession to the International Convention in Brussels in 1925; the publication of an alphabetical index containing the names, synonyms and Romanian descriptions of the products. (3)

**Sixth Edition of Romanian Pharmacopoeia**





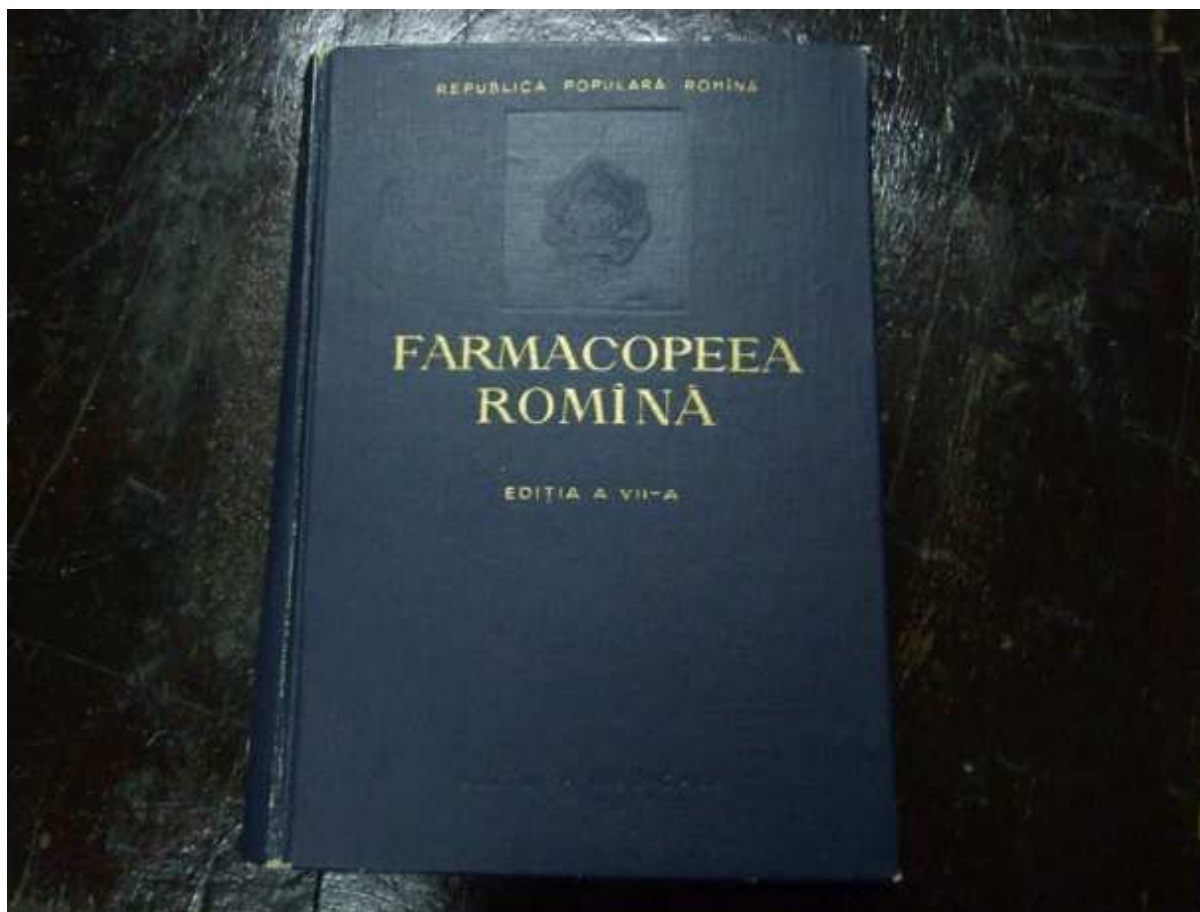
**The Sixth Edition of Romanian Pharmacopoeia** appears after the Second War, 5 years after the fifth edition in 1948, at the initiative of the Ministry of Health, which requested the Pharmaceutical Institute to elaborate a new edition.

The Commission working on the development of the volume included several professors, among which I. Vintilescu, C.N. Ionescu, N. Ioanid, Al. Mavrodin, and other pharmacists. While the new edition does not bring major changes, 50 new monographs are introduced and only 5 are removed. New vegetable drugs are formalized (Radix Primulae, Folia Stramonii, etc), both from the indigenous flora and imported.

As a novelty, two antibiotics are introduced (penicillinum calcicum și Penicillinum sodicum), a few sulfonamides are added and the monographs of a couple of vitamins (B2 and C) are completed.

The reason behind the reappraisal of the edition was the upgrading of the Medicine Control methods and the introducing of a group of monographs for the new drugs of the era. The volume contains a total of 722 monographs, out of which the chemical substances are dominant.

## Seventh Edition of Romanian Pharmacopoeia



**The Seventh Edition of Romanian Pharmacopoeia** was conducted by the Research Institute of Bucharest in collaboration with the Faculties of Pharmacy in Bucharest, Cluj, Targu Mures, as well as Dr. I. Cantacuzino Institute, Faculty of Veterinary Medicine the Pharmaceutical Research Institute branch in Cluj. The Commission included a total of 23 specialists under the guidance of professor C.N. Ionescu. Review work began in 1952 and ended in **1956**.

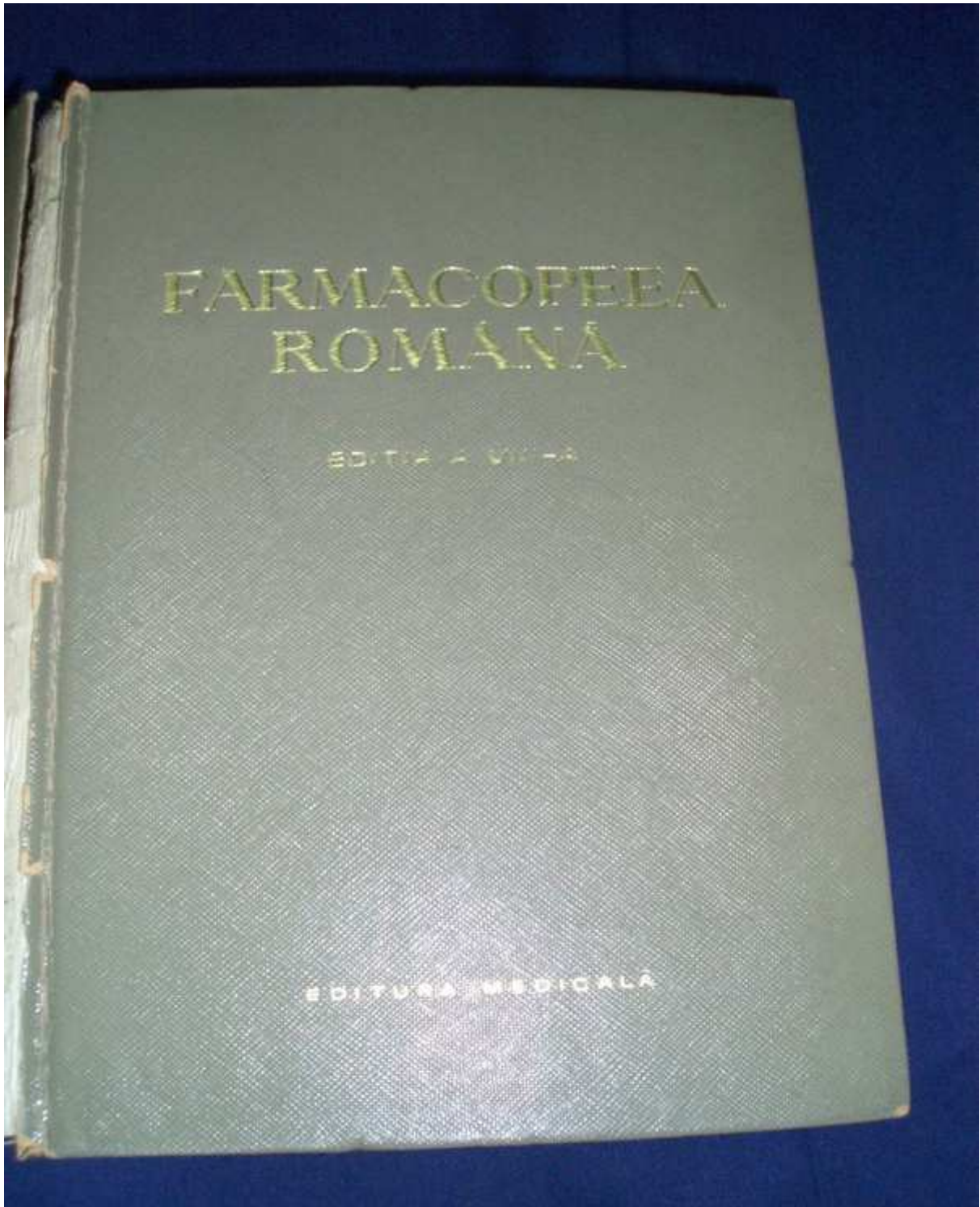
This edition introduces 12 new vegetable and animal products and 71 substances as well as a large number of galenical preparations, it adds monographs for tablets (13), tinctures (6), extracts (8), 7 solutions, 2 ointments, 4 syrups and 12 injections.

For many of the galenic preparations the imported ingredients were replaced with indigenous ones or similar, for example: Radix Senegae syrup was replaced with Radix Primulae.

As a novelty, this edition formalizes pharmaceutical substances recently introduced in therapy, like aureomycin, streptomycin, cloromycetin, as well as sulfonamides (sulfacetamide) and biological products as heparin and progesterone [3].

Compared to previous editions, this Romanian Pharmacopoeia introduces the structural formula in the monographs of organic compounds, besides the gross formula. For a more accurate assessment of purity, standards of colors have been introduced and approved. The volume also provides volumetric units for volume (liquid). For the first time, several collective desires for the drafting of the pharmacopoeia to include a chapter of serums and vaccines both for human and veterinary usage have been materialized. This edition contains 668 monographs out of which 444 are medicinal substances (66%).

## **Eighth Edition of Romanian Pharmacopoeia**



**The Eighth Edition of Romanian Pharmacopoeia** was made in **1965**. The responsibility of the elaboration of this new edition belongs to the Institute of Medicine State Control which published “Guidelines for Writing Monographs in RP VIII” in 1960 [3]. Several meetings and conferences took place around the country with the purpose of elaboration and standardization of future monographs. The technical and editorial commission consisted of 9 committees comprising 50 members and other collaborators. The completion of writing was made by a committee headed by professor P. Ionescu Stoian (V. Stănescu, N. Stanciu, I. Cruceanu,

Paulina Grințescu and Irina Ionescu). The 8<sup>th</sup> edition of the pharmacopoeia included 622 monographs out of which 183 were new preparations like corticosteroids, antibiotics, tranquilizers, and antihypertensives. This edition eliminates 230 monographs of products which were considered obsolete. However, imported medicines used successfully throughout the country were formalized.

The Latin names of inorganic substances are kept, but a new Latin label is added as well as the Romanian translation. For the organic substances, the international common name (ICN) is used next to the Romanian translation. Simplified methods have been introduced for their identification process, while for the organic substances which were not prescribed specific reactions, the identification of specific groups, according to existed reagents, was recommended.

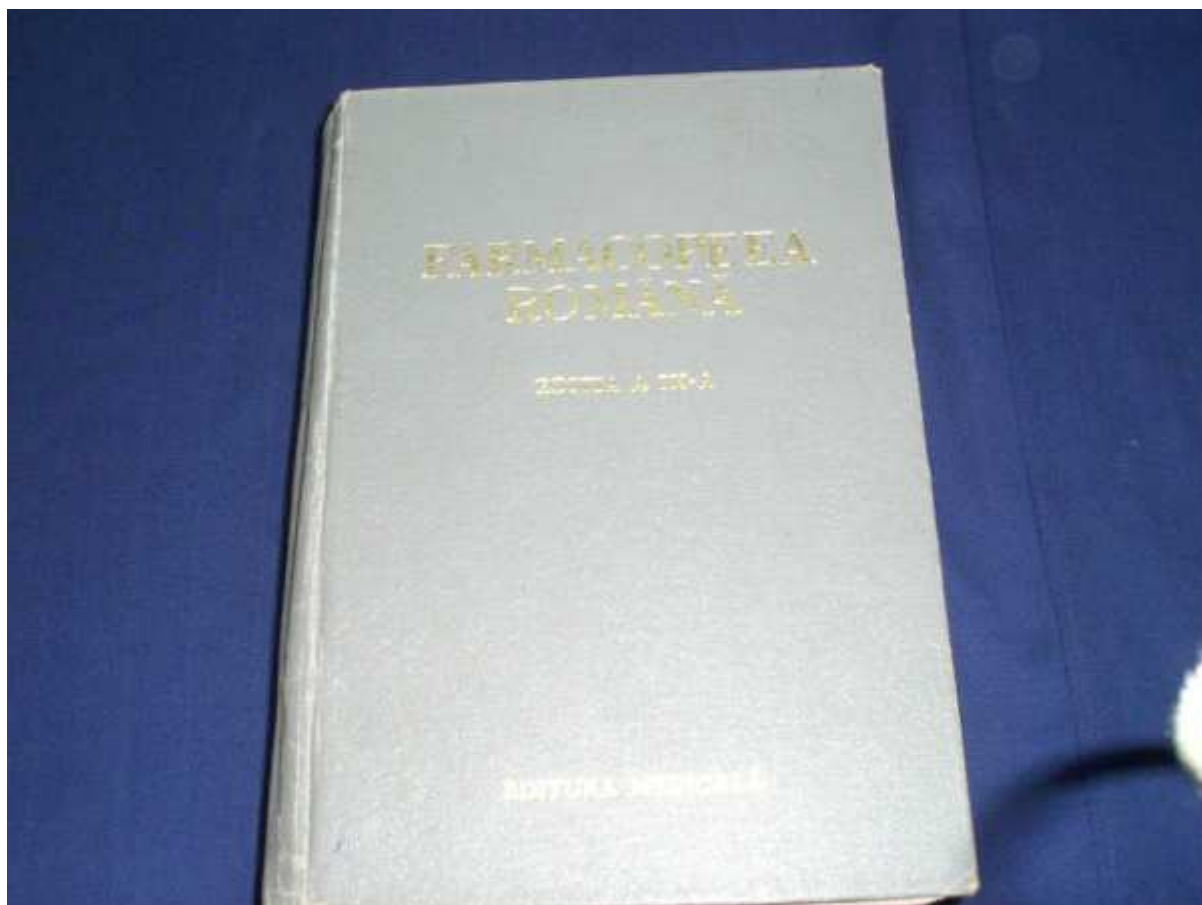
In the chapter concerning purity, monographs were completed with techniques regarding acidity and alkalinity limits, extending pyrogenic substances to other substances besides injectable solutions. Compared to the previous edition, volumetric measurements was dropped in favor of weighting. The volumetric system is kept for injectable solutions only. A separate chapter for toxicity and tolerance determination is introduced. This edition also introduces international standards and reference materials.

### Supplements of the 8<sup>th</sup> Pharmacopoeia



With a total of 946 pages, the 8<sup>th</sup> Romanian Pharmacopoeia is followed by three supplements as follows: first supplement printed in 1968 - introducing 25 new monographs. Its 130 pages also recommend the spectrophotometric method in several substances and preparations checking. The volume also introduces tables containing international common names and usual and maximum dosage for adults. The second supplement of the 8<sup>th</sup> Pharmacopoeia was edited in 1970 and it formalized the spectrophotometric method in ultraviolet and the spectral analysis (it only has 71 pages). The third supplement of RP VIII contains 155 pages which introduced new analytical methods and extended the other methods.

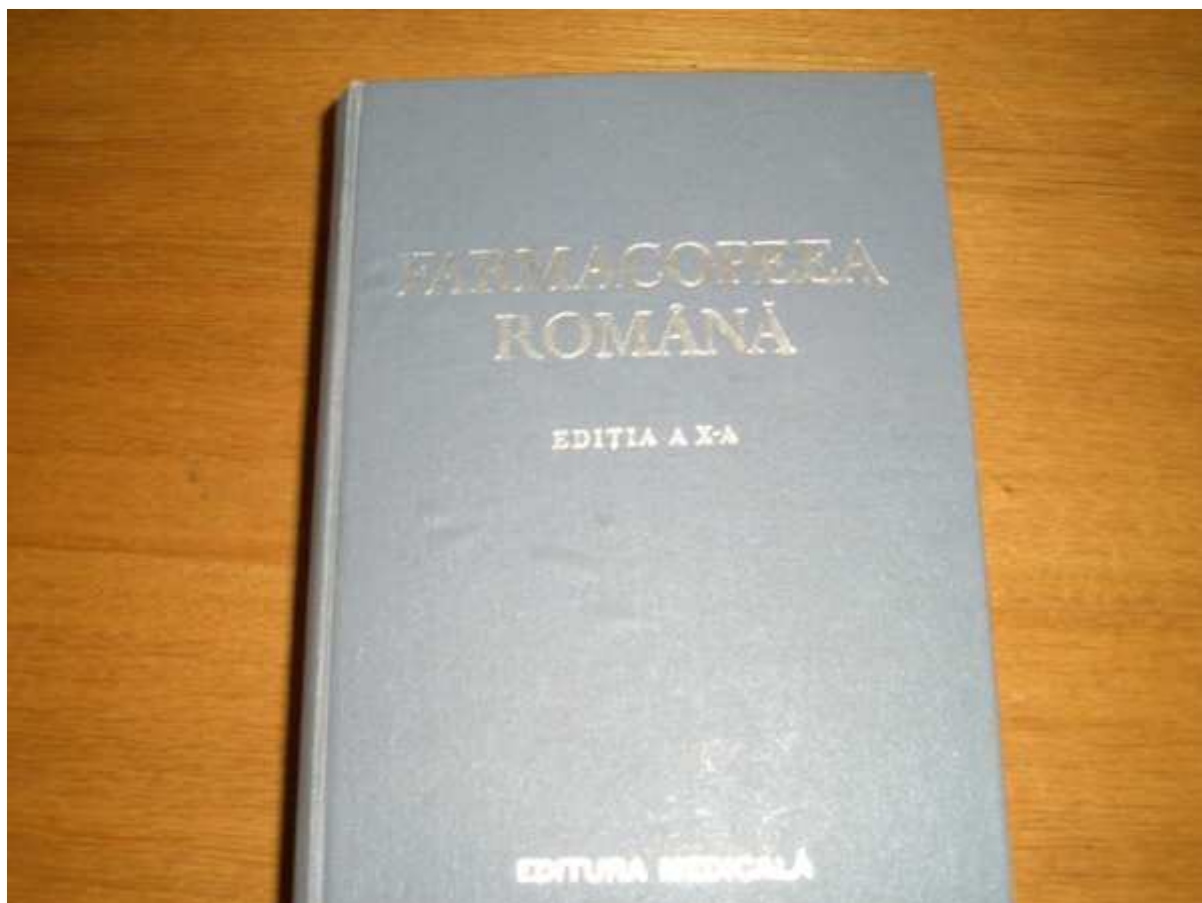
## Ninth Edition of the Romanian Pharmacopoeia



**The Ninth Edition of the Romanian Pharmacopoeia (RP)**, published in 1976, was developed by several committees of experts under the guidance of Professor P. Ionescu Stoian. As in the case of previous editions, some monographs are eliminated and others are introduced. Part of the last ones are several antibiotics (Rifampicinum, Kanamycinum sulfas, Cloxacillinum natrium etc), plasma substitutes (Dexreanum 40, dextranum 70), hormones (Hydrocortisonum, Prednisoni acetas). This edition adopted the international nomenclature for inorganic compounds, reason for which, in the Latin name of the products the cation is specified first and the anion after (Calcii chloridum). The 8<sup>th</sup> edition also has a supplement elaborated in 1981 by a group which included: Prf. C. Baloescu, Dr. pharm. I.Cruceanu and pharmacists Călin Georgeta, Grasu Angela, Jecu Maria. The supplement introduces new monographs (26), out of which substances (17) and pharmaceutical formulations (9) and it also completes the pharmacopoeia with standards and reference materials.

Edited in 1981 by the Medical Publishing House of Bucharest, the **RP IX Supplement** includes a general method of analysis, 5 national standards and 17 reference substances and it changes the name of 'national substandard' into 'national standard'. The table containing maximum dosage for adults information is modified and completed, cancelling the correspondent table in RP IX and becoming the only valid one. The supplement contains amendments and additions to some monographs as well as some general methods of analysis for the improvement of various quality parameters and the specifications of working approaches. The general monograph *Comprimata* states that the disintegration time for tablets should be of 15 minutes. The supplement was developed by a large group of pharmacists and the editing staff was coordinated by Prof. C. Baloescu. (ICSMCF).

## Tenth Edition of the Romanian Pharmacopoeia



**The current Edition of the Romanian Pharmacopoeia, the 10th, applicable since 1993, consists of 1315 pages, representing a large amount of information. As novelties, we mention the following:**

- Updating a large number of general monographs;
- Introduction of dissolution 'in vitro' test
- Completion of methods of analysis with:
  - i) Control of antimicrobial preservatives efficiency;
  - ii) Pressurized liquids chromatography;
  - iii) Disintegration, dissolving and dosage of tannins in vegetable products; atomic absorption spectrophotometry;
- 94 new monographs are introduced;
- 166 monographs are eliminated as well as 9 methods of analysis;
- The International System of Units (ISU) is adopted;
- Several monographs Latin titles have been modified, in accordance with OMS requirements (Lists for DCI);
- Table with maximum therapeutic doses were completed with usual therapeutic doses.

Despite all the modifications brought by the 10th edition of the Romanian Pharmacopoeia (RP X), three more supplements were published after. Hence, in **2000, Supplement I for RP X**

appears, introducing as novelty materials for containers for pharmaceutical usage, therapeutic usage recipients as well as reagents and standard solutions.

In **2004, the 2<sup>nd</sup> Supplement for RP X** is edited which contains 313 pages and formalizes the International System of Units (ISU) used in the RP and other units. This supplement also includes general chapters and individual and general monographs translated from the European Pharmacopoeia (EP), 4<sup>th</sup> edition. Monographs contained by the supplement from 2004 are of: capsules, tablets, pencils, granules, masticable medicinal chewing gums, auricular preparations, oromucosal preparations, inhaling preparations, pressurized pharmaceutical preparations, liquid preparations for external application, oral usage liquids, ophthalmic preparations, parenterals, irrigation preparations, rectal preparation, cutaneous semisolid preparations and many more. The update provided in this supplement contains some revised texts regarding: tablet disintegration, uniformity of mass dose preparations, materials based on unplasticized polyvinyl chloride for uninjectable liquid solution conditioning and for solid formulations administered orally. The supplement also presents tables containing Standard Romanian terms and tables containing types of packaging, closure systems and administration information.

In **2006, the 3<sup>rd</sup> Supplement for RP X** is published. The novelties of this supplement are: 'Introduction to the European Pharmacopoeia, 5<sup>th</sup> edition', new analytical methods, pharmacotechnical methods, alcoholmetric tables, tables of physical characteristics of radionuclides in EP. This supplement also presents a chapter concerning 'Compliance pharmacopoeias', and homeopathic preparations as well as updated standard Romanian terms.

## **Bibliography:**

1. M. Cotrău- Medicamentul de-a lungul vremii. Ed. Apollonia – Iași 1995.
2. V. Lipan – Istoria farmaciei române în date , Ed. Farmaceutică, 2009;
3. Josif Spielman, Gratiela Baicu – Istoria științelor farmaceutice în România Ed. Medicală AMALTEA 1994;
4. Farmacopea Română ediția I-a Ed. la Imprimeria statului, 1893- 790p
5. Farmacopea Română ediția a II-a Imprimeria Statului, 1874-160 p;
6. Farmacopea Română ediție a III-a Imprimeria statului, 1893 – 490 p;
7. Farmacopeea Editie speciala, 1915, - 712 p
8. Farmacopea Română ediția a IV-a; Atelierele grafice SOCEC &Co., Societate Anonima (Bucuresti) 1926.-570 p.
9. Farmacopea Română ediția a V-a; Ed. Tiparul Românesc 1943.- 539 p.
10. Farmacopea Română ediția a VI-a “Editată de Institutul Farmaceutic Bucuresti” 1948- 660 p;
11. Farmacopea Română ediția a VII-a, Editura Medicală din Bucuresti 1956.944 p;
12. Farmacopea Română ediția a VIII-a, Farmacopea Română ediția a VIII-a, 1965-946 p;
13. Supliment I F.R. VIII., Editura Medicală din Bucuresti 1968 – 130 p;
14. Supliment II F.R. VIII- Editura Medicală din Bucuresti,1970 – 71 p;
15. Supliment III F.R. VIII- Editura Medicală din Bucuresti,1972- 155p ;
16. Farmacopea Română ediția a IX-a, Editura Medicală din Bucuresti 1976 – 1005p;
17. Supliment I F.R. IX., Editura Medicală din Bucuresti 1981;
18. Farmacopea Română ediția a X-a, Editura Medicală din Bucuresti 1993 – 1315p;
19. Supliment I F.R. X., Editura Medicală din Bucuresti 2000 – 158p;
20. Supliment II F.R. X., Editura Medicală din Bucuresti 2004 – 310p;
21. Supliment III F.R. X., Editura Medicala din Bucuresti 2006 – 370p;