3. PHARMACOPEIA ANALYSIS

4.1 GENERAL INFORMATIONS

Pharmacopoeia word *(in ancient Greek; pharmakopoiia)* means to make drugs according to a law. Tanım olarak farmakope ilaç üretiminde kullanılan etkin ve yardımcı maddelerin nitel ve nicel çözümleme yöntemlerinin yer aldığı yasal ve bilimsel olarak uyulması gereken ulusal ve uluslararası kuralları ve yöntemleri içeren resmî kitaptır.

Inclusion of a substance in a pharmacopoeia does not indicate that it is either safe or effective for the treatment of any disease. However, the success of the treatment depends on the activity of the active substances used, as well as purity and standardization of active substances which present in medicines prepared both magistral and officinal form. In addition, in terms of treatment safety, the medicines should be prepared in accordance with certain rules, with the active substances which have certain criterias and all of the proses should be investigatable.

Tarihi gelişim içinde, tıpta kullanılan majistral ilaçların ve ofisinal preparatların sayısı arttıkça, bunların yukarıda sözünü ettiğimiz anlamda her yerde benzer ve aynı standartta hazırlanma zorunluluğu kendini iyice hissettirmeye başlamış ve bu konuda resmi ve yasal nitelikleri olan yazılı bir dökümanın gerekliliği, ilk Farmakope' leri gündeme getirmiştir.

İlaçların hazırlanmasına ilişkin ilk yazılı döküman, M.S. I. Yüzyılda LARGUS'un yazdığı ; COMPOSITIONES MEDICANMENTORUM adlı kitaptır. 1321 yılında Fransada V. Philip, bir emirname ile eczanelerde aynı tipte ilaç hazırlanmasına yönelik ANDIDOTARIUM'un kullanılmasını şart koşmuştur. Bugünkü anlamda ilk farmakopenin, 1497 yılında RICEPTARIO FIORENTINO adı ile Floransada basıldığı bilinmektedir. Bu tarihten sonra, yöresel ve bireysel farmakopelerin (*1565-Ausburg, 1628-Londra, 1636-Lyon, Pharmacopeia Internationalis of Leremy-1690, Pharmacopeia de Quincy vb.)* yaygınlaştığı görülmektedir. 18.Yüzyıl'ın sonları ve 19.Yüzyıl'ın başları ise, ilk ulusal farmakopelerin ortaya çıktığı dönemdir. Bunlar arasında, *İsviçre Farmakopesi (1775), Pharmacopeia Bativa-Hollanda (1805), Pharmacopeia Française-Fransız (1818), British Pharmacopeia-İngiliz (1864) ve Deutsche Arzneibuch-Alman (1890)* farmakopeleri sayılabilir.

The first Turkish pharmacopoeia was written in 1844 under the title of Pharmacopea Castrensis Otomana (Pharmacopee Militaire Ottomanee = Military pharmacopoeia) by Austrian Dr. Charles Ambrosie Bernard.

First pharmacopoeia of the period of Turkish Republic was published in 1930 under the title of Turkish Codex. The second was published in 1940 under the same title. Also a supplement of pharmacopoeia was published in 1948. The fourth codex of the Turkish Republic, which is the third edition of the 1948 codex, was published in 1954. In 1972, the title of Turkish Codex was changed to the Turkish Pharmacopoeia. The latest Turkish Pharmacopoeia in Turkey was prepared in 1974.

"The Convention on the Elaboration of a European Pharmacopoeia" was adopted by the Council of Ministers' decision dated 6 September 1993 and was published in the Official Gazette dated 10 October 1993 and numbered 21724 and enacted with the number 19461 and entered into force on 22 February 1994. Since that date, Turkey is a member of The European Pharmacopoeia Commission.

The first volume of the sixth pharmacopoeia of the period of the Turkish Republic was published in 2004 as the Adoption of the European Pharmacopoeia Volume 1.

Nowadays, the most commonly referenced pharmacopoeias are:

European Pharmacopoeia
British Pharmacopoeia
American Pharmacopoeia
Martindale

British Pharmacopoeia

British Pharmacopoeia (BP), is an annually published collection of quality standards for UK medicinal substances. It is used by individuals and organisations involved in pharmaceutical research, development, manufacture and testing. The British Pharmacopoeia is an important statutory component in the control of medicines which complements and assists the licensing and inspection processes of the Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom.

The regulation of medicinal products by officials in the United Kingdom dates back to the reign of King Henry VIII (1491–1547). The Royal College of Physicians of London had the power to inspect apothecaries' products in the London area, and to destroy defective stock. The first list of approved drugs, with information on how they should be prepared, was the London Pharmacopoeia, published in 1618. The first edition of what is now known as the British Pharmacopoeia was published in 1864, and was one of the first attempts to harmonise pharmaceutical standards, through the merger of the London, Edinburgh and Dublin Pharmacopoeias. In 1907, the British Pharmacopoeia was supplemented by the British Pharmaceutical Codex, which gave information on drugs and other pharmaceutical substances not included in the BP, and provided standards for these. British Pharmacopoeia is now used in over 100 countries. Australia and Canada are two of the countries that have adopted the BP as their national standard alongside the UK.

The British Pharmacopoeia comprises six volumes. Content of them;

Volumes I and II

- Medicinal Substances

Volume III

- Formulated Preparations
- Blood related Preparations
- Immunological Preperations
- Radiopharmaceutical Preperations
- Surgical Materials
- Homeopathic Preperations

Volume IV

- Appendices
- Infrared Reference Spectra
- Index

Volume V

- British Pharmacopoeia (Veterinary)

Volume VI (CD-ROM version)

Martindale

Martindale (The Complete Drug Reference) is a reference book that covers all kinds of information on medicines and excipients that clinically important anywhere in the world.

Martindale includes some 6,000 medicines used throughout the world, details of over 180,000 proprietary preparations. It also includes almost 700 disease treatment reviews.

Martindale was first published in 1883 under the title Martindale: The Extra Pharmacopoeia. Martindale contains information on drugs in clinical use worldwide, as well as selected investigational and veterinary drugs, herbal and complementary medicines, pharmaceutical excipients, vitamins and nutritional agents, vaccines, radiopharmaceuticals, contrast media and diagnostic agents, medicinal gases, drugs of abuse and recreational drugs, toxic substances, disinfectants, and pesticides.

Martindale is arranged into two main parts followed by three extensive indexes. In the monographs section; there are more than 6000 substances, their nomenclature, properties and effects of each substances. This section covers excipients, herbals, some toxic substances and drugs no longer clinically used but still of interest in addition to the active ingredients. In the preparations section; there are over 180 000 items from 43 countries and regions. In addition, there are a section titled directory of manufacturers, a section which contains pharmaceutical terms in various languages, and a general index section which prepared from 175,000 entries and includes approved names, synonyms and chemical names.

Martindale, which nowadays published by Pharmaceutical Press, has advantages than other pharmacopoeias such as covering detailed, reliable and objective information, providing extensive information in international scale and being acceptable worldwide.

Martindale is prepared with items from 43 countries and regions by using 54 000 references.

Martindale provides a useful source of information for patients arriving from abroad to identify their existing medication, with the section of pharmaceutical terms in different languages. This may reveal that a currently taken proprietary preparation is available under another brand name.

In the digital version of Martindale, more monograms and preparates can be found.

The United States Pharmacopeia

The United States Pharmacopeia (USP) is official pharmacopeia of the United States and published in a combined volume with the National Formulary as the USP-NF. It was first published in 1820.

The United States Pharmacopeial Convention (usually also called the USP), is a nonprofit organization that owns the trademark and also owns the copyright on the pharmacopeia itself and published USP-NF annualy.

Prescription and over-the-counter medicines and other health products sold in the US must comply with USP-NF standards. USP also sets standards for dietary supplements and food ingredients.

Many other countries use the USP-NF instead of issuing their own pharmacopeia, or to supplement their government pharmacopeia.

European Pharmacopoeia

The European Pharmacopoeia of the Council of Europe is a pharmacopoeia which lists a wide range of active substances and excipients used to prepare pharmaceutical products in Europe. Different chemicals, antibiotics, biological substances; vaccines for use in humans and animals; immunological serum; radiopharmaceutical preparations; herbal medicines; more than 2000 specific and general monographs including homoeopathic preparations and homeopathic stocks. It also includes dosage forms, General monographs, properties of Materials and Containers; 268 methods are given with the form or chromatograms and 2210 reagents are described. Monographs provide quality standards for all essential drugs used in Europe. All medicines sold in the 38 member states of the European Pharmacopoeia must comply with these quality standards so that consumers have a guarantee of products from pharmacies and other legal suppliers.

The first edition of the European Pharmacopoeia was published in 1967 as a single volume. Since its 5th edition, published on June 15, 2004, it has been published in 2 volumes. The latest up-to-date version currently in use is the 8th edition and was released in January 2014.

European Pharmacopoeia, including Turkey, the United Kingdom, Ireland, Belgium, Austria, Denmark, Germany, France, Greece, Italy, Spain and many other countries, was issued a protocol signed under the auspices of the European Union (European Treaty Series No. 134). Due to European Pharmacopoeia is current pharmacopoeia for Turkey, our explanation will be more for this pharmacopoeia. Two basic committees have been established in the preparation of the European Pharmacopoeia for which a joint publication decision has been made between these countries;

1- Public Health Commission
2- The European Pharmacopoeia Commission

The Public Health Committee have the right to control the function of the European Pharmacopoeia Committee, to reject or to approve their decisions partially. It also has the authority to control the functions of the pharmacopoeia committee.

The European Pharmacopoeia (Ph. Eur.) Commission is the decision-making body of the European Pharmacopoeia and is responsible for the elaboration and maintenance of its content. The Ph. Eur. Commission adopts all the texts to be published in the Ph. Eur. and takes technical decisions by consensus.

The purpose of the European Pharmacopoeia is to promote public health by the provision of recognised common standards for the quality of medicines and their components.

Monographs and other parts of the European Pharmacopoeia are arranged according to the needs. These are health rules and quality control practices organized by experts.

The European Pharmacopoeia consists of two main parts.

1- General Chapters
    a- General notes
    b- Analysis methods
    c- Storage materials and storage containers
    d- Reagents
    e- General tests
2- Monographs

4.1.1 General Chapters

It is organized as a different section from the monographs and it is a technical guideline that gives more information for the implementation of many methods.

General Chapters provide the basic principles and rules on many issues such as patent rights, the ethics of experimental animal use and its rules, hydrates, chiral substances, polymorphism, quantification specifications, impurities, hygiene standards of medical devices, provide .

Patents: This section in the pharmacopoeia, where patent protection issues are identified, includes principles such as who may use the patent other than the original owner and what their rights are or how these rights are granted.

Experimental animal use: The Commission recommends that as far as possible, animal use should be reduced in pharmacopoeia tests and alternative methods should be seek in the field. Some other suitable methods have been proposed by the commission in accordance with the pharmacopoeia purposes.

Hydrates: The degree of water refers to those containing more than one form in the pharmacopoeia, as indicated in the headings of the monographs.

Chiral subtances: For all chemical compounds containing asymmetric carbon atoms, a optical rotation (the degree of rotation) test is envisaged. This test shows that the specific rotational angle of the racemic mixture or a specific enantiomer contained in the monograph.

Polymorphism: Polymorphism of a substance usually depends on its character. Generally, monographs do not provide information for a particular crystal form of the compounds. In some cases, the crystal form must be predetermined. For example; for dosage forms, the manufacturer may need to use a special crystalline form and ensure that the crystal form of the substance is used in production.

Quantification specifications: The main objective for the preparation of monographs of chemicals is to ensure that impurities are controlled by well-designed tests. In this way, the monographs are designed to satisfy all requirements and ensure the quality of the product.

Impurities: Many monographs list the potential impurities identified through tests published in recent years. Known impurities (also known as active impurities) can be observed in material boilers. Potential impurities can be expected during fabrication. The impurities formed during fabrication can be compared with the evaluation lists given in the monographs.

Medical devices: In all of pharmacopoeias, medical supplies; There are monographs published especially for surgical instruments and clothes used for this purpose.

a- General notes

This section contains information about volumetric containers and volumetric methods, water baths, limits of quantitative measurements, drying conditions and criteria. For example; it is the rule that the weighings allow a change of ±10 and in the expression of volumes, the units after the zero should be used as 10.0 ml or 0.50 ml.

b- Analysis methods

• The standards of the devices used (drippers, standards of UV lamps for analytical purposes, tubes used in comparison tests),
• pH measurement and identification standards,
• Indicators and color ranges at specific pHs,
• Refractive index standardization,
• Optical rotation (angle of rotation) measurement and standardization,
• Viscosity measurement and standardization- tools used,
• Melting point determination methods,
• Freezing point determination methods,
• Potentiometric titration,
• Fluorimetry test methods,
• Test methods with atomic absorption spectrometry,
• Test methods with atomic emission spectrometry,
• IR absorption spectrometer,
• UV and Visibl UV absorption spectrometer,
• Paper chromatography and TLC,
• Gas chromatography and liquid chromatography techniques,• Elektroforez,
• NMR spectroscopy,
• X-ray fluorescence spectrometer,
• Condactometry,
• Identification reactions and quantitation of ions and functional groups (acetates, acetyl, alkaloids, aluminum, ammonium, antimony, arsenic, barbiturates, benzoates, bismuth, carbonates and bicarbonates, chlorides, citrates, esters, iodides, lactates, iron, magnesium, mercury , nitrates, potassium, salicylates, silicates, silver, sodium, sulphates, tartates, xanthines, zinc etc.).
• Identification of fatty acids by TLC,
• Identification of phenothiazines by TLC,
• Identification of odor,

• Boundary tests (ammonium, arsenic, calcium, phosphates, sulfates, chlorides, magnesium, heavy metals, iron, potassium, aluminum, free formaldehyde, alkaline impurities in fatty acids, antioxidants in fatty acids, determination of sterols in fatty acids with TLC and GC)

• Biological tests (sterility, various cell cultures, vaccines, pyrogen tests, abnormal toxicity tests, allergy tests, possible microbial contamination in products, identification methods and materials for bacterial endotoxins, activity tests for immunoglobulins, immunochemical methods for biological quantitation, antibiotics microbiological quantitation, quantitation of corticotropin, quantitation of blood coagulation factor VIII, quantitation of heparin, quantitation of diphtheria vaccine, quantitation of tetanus vaccine, quantitation of immunoglobulins)

• Methods applied in pharmacognosy (foreign matter definition, water in essential oils, solubility of essential oils in alcohol, identification of essential oils in vegetables, determination of pesticide residues)

• Pharmaceutical technical methods (disintegration of tablets and capsules, disintegration of suppositories, solubility from solid dosage forms, solubility in transdermal preparations, fragility in coated tablets, test of resistance of tablets)

c- Storage materials and storage containers

Standardization of various storage containers (polyethylene, polypropylene etc.), standardization and tests of storage containers of blood products; resistance of glass containers to centrifuge, resistance to hydrolytic pressure, resistance to heat shock; plastic containers and standardizations; information on the standardization of sterile plastic containers for blood products and components.

d- Reagents

Necessary substances for the preparation of buffer solutions and standard solutions and their properties are mentioned.

e- General tests

There are prepation methods of sterile products, various sterilization methods (terminal sterilization, filtration and filtration conditions, determination of antimicrobial sterilization and efficacy, sterilization of vaccines and determination methods) in this section.

4.1.2 Monographs

This is the part that all properties of the drug is given. Physical and chemical properties of the drugs, their solubility, quantifications, identification reactions, storage conditions and use are included. The chemical composition, molecular formula and molecular weight of an officinal substance are written at the beginning of the monograph.

Officinal drugs are given in Pharmacopoeia as monographs.
Officinal drugs: (of pharmaceutical products) available without prescription.
Officinal drugs: (of a plant) having pharmacological properties.

Magistral drugs are medicinal products prepared in a pharmacy for an individual patient in accordance with a prescription from a doctor.

Proprietary medicine is drug that prepared in the state or private sector factories and readily available in the pharmacy.

See the Pharmaceutical Chemistry Practices III for the identification reactions, odor, taste and solubility of officinal drugs in monographs.

QUESTIONS

1) How many parts of the European Pharmacopoeia? Write as items.
2) What is the name given to all the properties of the drug in pharmacopoeia? What are the features of the drug in this section?
3) What are the most referenced pharmacopoeias nowadays? Write as items.