PHARMACY LAW

What is a Medicinal Product?

Article 1 of the '***Pharmaceutical and Medical Preparations Law- Law No. 1262***' and Article 4 of the '**By-Law on the Registration of Medicinal Products for Human Use**'

When you ask people about their perception of a drug, they will likely respond….

They tend to answer a drug is a product that imporoves one's health and intended for use with a disease.

Medicinal product for human use is described as any natural and/or synthetic origin active substance or combination of substances administered to human beings with a view to treating and/or preventing a disease, making a diagnosis, correcting or modifying a physiological function.

What is a Food?

Article 3 of the '*The Food Law- Law No. 5179*'

Food is any substance which the human consumes and drinks in fresh, cooked, raw or processed form, except tobacco and drugs.

What is a Food Supplement?

Article 4 of the *'By-Law on the Importation, Production, Processing and Supply of Food Supplements'* which was published on the *Official Gazette* No. 28635 on 2 May 2013, came into force on 2 August 2013 and was amended on 21 November 2015 and 28 March 2017.

Food supplements are defined as products prepared in the form of capsules, tablets, powder packets for single use, liquid ampoules, dropping bottles or other liquid and powder forms of nutritional elements such as:

- **Vitamins.**
- **Minerals.**
- **Proteins.**
- **Carbohydrates.**
- **Fibres.**
- **Fatty acids and amino acids.**
- **Plants with nutritious and physiological effects.**
- **Substances of herbal or animal origin with determined daily doses.**

Food Supplement versus Medicines: Marketing Process

Medications must pass clinical trials before being released to the public and the tests need to prove each drug is safe.

Food suuplements are not regulated by Ministry of Health. Ministry of Food, Agriculture and Livestock is responsible for food supplements.

Very simple and short application. This is called 'sales permit' not a 'licence'.

The general rule for supplements is they're considered safe until they're proven unsafe.

What is a Herbal Medicine?

A herbal product will be considered a medicinal product if medicinal claims are made about it i.e. that it can prevent, treat or cure disease.

- **Can be sold only in community pharmacies.**
- **Should be used under the supervision of a physician.**
- **With condition of the efficacy, safety and quality, they can be prepared in any dosage form.**
- **No advertisement and promotion via internat and media.**
- **Must past a clinical trial**

What is Traditional Herbal Medicinal Products?

Article 4 of the *'By-Law on Traditional Herbal Medicinal Products'* which was published on the *Official Gazette* No. 217721 on 6 October 2010.

Traditional Herbal Medicinal Products are defined as products that should be used at least fifteen years in Turkey or the European Union member countries, while in other countries it should be used for thirty years.

Bibliographic studies proving safety and effectiveness should be done.

These products were designed for the use without a prescription or treatment follow-up by a physician which have specific indications appropriate for complemantary medicines, and have only specific doses and specific treatments appropriate to the posology.

They can be administered by orally, externally, or inhalation.

Traditional Herbal Medicinal Product versus Medicine

According to *By-Law on Traditional Herbal Medicinal Products*, licensing of herbal medicinal products which have therapeutic effects on human health is made by Ministry of Health. However the present situation is not certain. Because at the same time sales permit of these products can be taken from Ministry of Food, Agriculture and Livestock.

As a result of these ambiguities, a product prepared from a medical plant is sold in pharmacies as an approved herbal medicine from the Ministry of Health; another product, prepared under the same medical nutritional supplement, can be sold at a point of sale within a large shopping mall, away from supervision.

What is a Cosmetic Product?

Article 4 of the '*Cosmetic Law- Law No. 5324*'

Cosmetic products are defined as the products that are intended to be applied to the outer parts of the human body; epidermis, nails, hair, lips and external genital organs, teeth and/or to oral mucous membrane thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance.

What is a Medical Device?

Article 3 of the '*By-Law on Medical Devices*' which was published on the *Official Gazette* No. 27957 on 7 June 2011.

The term medical device means an instrument, apparatus, implement, machine, contravince, implant or other materials, which is

- **Intended for use in diagnosis of disease or other conditions, or in the cure mitigation, treatment, monitoring, prevention of disease, searching, altering of an anatomical or physiological function in man,**
- **Intended to affect the structure or any function of the body of a man, and which does not achieve any of its principle purpose through chemical, pharmacological, immunological or metabolic action within or on the body of a man.**

FDA has stated that many factors may determine whether a product is a device or a drug:

- **Is the product intended to deliver drugs to the patient, but is not prefilled by manufacturer?**
- **Is the drug component included solely to make the product safer?**
- **Is the drug component intended to have a therapeutic effect?**

Marketing and Licensing of Medicinal Products

Licensing Authority

Licences are issued by the 'Licensing Authority' which for human medicines consists of Health Ministers of Turkey. In practice, of human medicines is handled by the Turkish Medicines and Medical Devices Agency (TMMDA).

The licencing of veterinary products is generally dealt with by the Ministry of Food, Agriculture and Livestock.

Marketing Authorization

According to Article 5 of the *By-Law on the* Authorization *of Medicinal Products for Human Use* which was published on the *Official Gazette* No. 25730 on December 17, 2005 prohibit the placing on the market of most medical products, unless they have a marketin authorization.

Under Article 16 of the *By Law on the* Authorization *of Medicinal Products for Human Use*, the following criteria must be taken into account by TMMDA when deciding whether to grant a marketing authorization for a human medicinal product:

- **Whether it is effective in its designated usage conditions.**
- **Whether the pharmaceutical product's safety has been proved.**
- **Whether the pharmaceutical product features the appropriate technical and pharmaceutical properties.**

- **Detailed requirements and a list of documents to be provided alongside the marketing authorization application are set out in Article 8 of the *By Law on the* Authorization *of Medicinal Products for Human Use*.**
- **The applicant must prepare a common technical document file (CTD) (OTD, in Turkish) and apply to the TMMDA. Details about the CTD file are stipulated in the guidelines issued by the Agency.**

Module1 is for administrative information.

Module 2 should also provide the overall summary of the 'quality' information provided, the non-clinical overview and the clinical overview, as well as the non-clinical written summaries and the tabulated summaries, and the clinical summary.

Module 3 contains information on quality topics.

Module 4 contains the nonclinical study reports.

Module 5 contains the clinical study reports.

The Process of Marketing Authorization

- **The preliminary evaluation period for a marketing authorisation application is 90 days.**
- **Except in extraordinary circumstances, once the preliminary evaluation period has ended, the Agency must issue a decision on the application within 210 days. However, in practice, obtaining a marketing authorisation for a new product in Turkey may take around two years.**
- **The Agency must decide for pharmaceutical products that meet any of the following criteria:**
  - **Are original.**
  - **Are innovative.**
  - **Would reduce public healthcare expenditure.**

The Process of Marketing Authorization

- **The procedure is often extended due to the Good Manufacturing Practices (GMP) certificate required by the Institution. Article 8 of the Licensing Regulation requires a GMP certificate for manufacturing facilities to be submitted with the application.**
- **The Agency issues the GMP certificate**

Period of authorisation and renewals

- **A marketing authorisation for a human medicinal product is granted for five years.**
- **To renew the marketing authorisation, information on the medical product's quality, safety, and effectiveness, along with pharmacovigilance data, must be submitted three months before the marketing authorization's expiration date.**
- **Failure to renew the marketing authorization within the five-year period does not automatically result in expiration of the marketing authorization. In practice, the renewal procedure for pharmaceutical products is not always followed, and certain products are currently marketed without renewing their authorizations.**

Three types of applications may be;

1. **New drug application**
2. **Generic Medicinal Product application**
3. **Biotechnological Medicinal Products application**

For placing the product on the market, the following additional regulations must be considered:

- ***By-Law on Safety of Drugs*** **(Safety Regulation) (*Official Gazette No. 28973 of 15 April 2014*). The Safety Regulation lists the activities conducted for monitoring, research, recording, archiving and assessing the safety of drugs for human use which have been granted registration or permit, as well as natural or legal persons conducting such activities.**
- ***By-Law on Packaging and Labelling of Medicinal Products for Human Use*** **(Labelling Regulation) (*Official Gazette No. 25904 of 12 August 2005*). It determines the procedures and essential information to be given on labels and packages.**

Responsibilities of the marketing authorization holder

Article 5 of the *By-Law on Safety of Drugs* describes the responsibilities of the marketing authorization holder:

- **assure the safety of its medicinal products. For this purpose, the marketing authorization holder is responsible to continuously monitor the safety of its medicinal products, notify the Agency of any changes that may have an effect on the risk-balance assessment of the medicinal product,**
- **establish a pharmacovigilance system to undertake pharmacovigilance,**
- **assemble a competent and appropriately qualified and trained personnel for the performance of pharmacovigilance activities,**
- **instructing healthcare providers to report any suspected adverse reactions to TÜFAM,**
- **appends a standard wording to the package leaflet, asking consumers to report any suspected adverse reactions to a healthcare professional or directly to TÜFAM.**

Pharmacovigilance: Science and activities relation to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem

Pharmacovigilance system: A system used by marketing authorization holders and applicants to fulfill the tasks and responsibilities listed in this *Regulation* and designed to monitor the safety of medicinal products and detect any potential changes to their risk-benefit balance.

TÜFAM: Turkish Pharmacovigilance Center, established within Turkish Medicines and Medical Devices Agency.

Responsibilities of healthcare professionals

Spontaneous reporting to TUFAM of adverse reactions to drugs occurring in patients is a professional responsibility of the healthcare professional observing such reactions.

Responsibilities of healthcare institutions and organizations

They should ensure most accurate reporting of adverse drug reactions to TUFAM at the earliest possibility, hospitals will establish and operate an internal pharmacovigilance system according to this Regulation.

The role of Agency

- **uses a pharmacovigilance system to gather information on drug-related risks.**
- **conducts activities, encouraging consumers and healthcare professionals to report any suspected adverse reactions that they encounter to TÜFAM.**
- **records suspected adverse reactions occurring in Turkey, reported by healthcare professionals or consumers, and forwards them to the World Health Organization's Center for Drug Monitoring.**
- **organizes basic training programs on pharmacovigilance.**
- **relays any reported cases of suspected adverse reactions to the marketing authorization holder within 15 days after the reporting date.**

Labeling requirements

Outer package: **The package into which the immediate package is placed.**

Immediate package: **The container in which the product is placed or the form of package directly in contact with the product.**

Labeling: **Information on the immediate or outer package.**

Package insert: **Written information presented with the product, prepared for the users.**

Summary of Product Characteristics (SPC): **The summary of the product characteristics contained in the medicinal product's marketing authorization dossier.**

According to *By-Law on Packaging and Labelling of Medicinal Products for Human Use* (*Official Gazette No. 25904 of 12 August 2005*).

What information that shall appear on the outer, immediate package, packege insert of the product is determined.

Clinical Researches

Clinical researches that are related to medicinal products, herbal medicinal products, and biological products are held according to *By Law on Clinical Researches of Drugs And Biological Products* which was published on the *Official Gazette* No. 28617 on April 13, 2013.

The purpose is to regulate the procedures and principles for conducting scientific researches on people within the framework of good clinical practices.

What is a Clinical Research?

It means the researches conducted on humans in order to reveal or confirm the clinical, pharmacological or other pharmacodynamical effects of one or more research products, to define the relevant adverse conditions or reactions, to determining absorption, distribution, metabolism and excretion and to study reliability and efficient aspects.

General Principles of a Clinical Research

Many conditions are sought for conducting such researches.

The basic principles sought in the researches are shaped basically by the protection of human's (volunteer) health, dignity, and rights.

Volunteer: The patient of health person participating in the clinical trial with a written consent taken from himself or his legal representative.

Supporter: It means the person- institution or organization responsible for commencing, conducting or financing the clinical research.

Ethical committee: It means the independent committees, which will be formed and approved by the Agency (TMMDA) for providing opinion regarding the methods and documents to be used while informing the volunteers, the consents to be taken from these people as well as other relevant issues regarding the research in order to protect the rights, safety and well-being of the volunteers.

These general principles can briefly be explained like below:

1. **Before conducting a research on a human, it is mandatory that the research should be conducted in a non-human test environment or over a sufficient number of test animals.**
2. **The scientific benefits expected from the research cannot be considered more important than volunteer's health or the possible risks that may emerge in terms of health care and other personal rights.**
3. **It is prohibited to apply methods that may cause pain to the volunteer in a way that doe not comply with human dignity during research.**

4. The objective of the research that is desired to be reached should be more than the inconvenience that it brings to the person the hazards it may cause to the health of the person.
5. Volunteer's consent is obtained completely based on his free will by «Volunteer Consent Form»
6. Volunteer can leave the research at his own will with or without justification and he cannot be subjected to any loss from his current rights during the medical monitoring.
7. The research SHOULD ONLY be started after getting the consent of the ethical committee.
8. It is necessary to make insurance for the volunteers against damages that may result from the clinical researches.

In the same regulation the conditions regarding participating of different kind of people is determined. These are:

1. **childeren,**
2. **pregnant women, puerparent women, and breastfeeding women,**
3. **limited people**
4. **unconsious people, and people in intensive care**

Article 10 of the *By Law on Clinical Researches of Drugs And Biological Products*

Clinical Research Periods

Phase I or 1st Period:

The research product is tried by being applied to *healthy volunteers* in sufficient number, or *to sick volunteers* in the cases when it is not possible to try the product on healthy volunteers, in order to determined pharmacokinetic qualities, toxicity and bodily functions of the research product in question

Phase II or 2nd Period:

The research product is tried by being applied on a *sufficient number of volunteering patients* with the purpose of researching the clinical efficiency and safety of the therapeutic dose limits of the research product.

Phase III or 3rd Period:

The research product, which passed Phase I and Phase II, is tried in terms of its efficiency, safety, possible new indications, different doses, new ways and methods of administer, new patient populations and new pharmaceutical manners by being applied on a *sufficient number of patients* chosen according to the qualities and nature of the research.

Phase IV or 4th Period:

This is the *clinical treatment period* in which the clinical treatment is applied on *many volunteering patients* in order to thoroughly investigate or compare the products in question with other treatment products and methods in terms of confirmed indications, posology and implementation manners of products licensed in Turkey and the safety and efficient of the authorized products regarding the recommended uses. (comparing stage with other products licensed in Turkey)

About the Location

Places in which clinical researches will be made have to have the following by taking basis the Good Clinical Research Practices Guide;

- **Sufficient number of personnel and equipment,**
- **Places and facilities required for the storage and distribution of the product,**
- **Facilities and equipment that can provide the appropriate care for the volunteers,**
- **Facilities and equipment that may make the transfer of volunteers to a more advanced heath institution,**
- **Facilities and equipment that may retain the documents and information regarding the volunteers and the research after the research is completed**

Other responsibilities of researchers and supporter

- **Responsible researcher should notify the supporter immediately about all the adverse conditions.**
- **Supporter must notify the ethical committee and the Institution about sever adverse reactions emerging during the research within seven days after obtaining such information at the latest.**
- **All the records regarding the research must be kept by the responsible researcher regularly and retained for at least four years after the research is completed in all the centers.**

By Law on Clinical Researches of Drugs And Biological Products

PART SIX is about:

- **Structure,**
- **Duties,**
- **Operational Procedures, and Principles of the *Ethical Committees***

PART SEVEN is about:

- **Structure,**
- **Operational Procedures, and Principles of *Clinical Researches Advisory Committee***

See you next week…