LAW ON MEDICINAL PRODUCTS AND MEDICAL DEVICES

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I GENERAL PROVISIONS

Article 1

This Law shall regulate medicinal products and medical devices for use in human medicine, conditions and manner for ensuring their quality, safety and efficacy, manner and procedures for their manufacturing, testing, placing on the market, marketing, pricing, quality control, advertising and inspection.

This Law shall also regulate narcotics and psychotropic substances, and precursors needed for manufacture of medicinal products or medical devices provided that they are not regulated by a separate law.

Article 2

For the purpose of this Law the following definitions will be used:

1. MEDICINAL PRODUCT is any substance or combination of substances, presented as having properties for treating or preventing disease in human beings. Medicinal product is also any substance or combination of substances which may be used in or administered to human beings with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

2. SUBSTANCE is any matter irrespective of origin which may be:

- Human, e.g. human blood, human blood products.
- Animal, e.g. micro-organisms, whole life organisms, parts of organs, animal secretion, toxins, extracts, blood products
- Herbal, e.g. micro-organisms, plants, parts of plants, herbal secretions, extracts,
- Chemical, e.g. elements, naturally occurring chemical materials and chemical products obtained by chemical change or synthesis, and
- Obtained through biotechnological procedure.

3. ACTIVE SUBSTANCE is a pharmacologically active ingredient in a given pharmaceutically dosed form.

4. EXCIPIENT is any substance other than the active substance which is included in the manufacturing process or contained in a finished pharmaceutical form of a medicinal product

5. PHARMACEUTICAL FORM is a form of medicinal product suitable for its application (tablets, capsule, ointments, solutions for injections, etc.).

6. MEDICINAL PRODUCT BATCH is a specific quantity of any medicinal product produced in the course of one manufacturing cycle whose homogeneity is fully guaranteed.

7. NAME OF THE MEDICINAL PRODUCT is the name that may be either an invented name which does not cause confusion with the common name, or a common or scientific name accompanied by a trade mark or by the name of marketing authorization holder.

8. COMMON NAME is the international non-proprietary name (INN) recommended by the World Health Organization or, if one does not exist, the usual common name.

9. BIOLOGICAL MEDICINAL PRODUCT is any medicinal product which as active substance contains biological substance or substance obtained thorough procedure which includes biological systems. Biological substance is any substance obtained from or using biological source and which needs combination of physical and chemical and biological investigations for reaching quality, together with the procedure for preparation and supervision. These are, for example, medicinal products prepared using biological or biotechnological procedure, including cell cultures and recombinant DNA technology, blood and plasma medicinal products, immunological medicinal products etc.

10. IMMUNOLOGICAL MEDICINAL PRODUCT is a medicinal product consisting of vaccines, toxins and serums or allergen products.

11. MEDICINAL PRODUCT DERIVED FROM HUMAN BLOOD OR HUMAN PLASMA is any medicinal product based on blood constituents (albumin, coagulating factors and immunoglobulins).

12. BLOOD AND BLOOD COMPONENTS are preparations manufactured from blood; they shall not be considered medicinal products within the context of this Law and are used as raw materials for industrially manufactured medicinal products that under this Law do not require marketing authorization.

13. RADIOPHARMACEUTICAL PREPARATION is any medicinal product which, when ready for use, contains one or more radionuclides (radioactive isotopes) intended for a medical purpose.

14. RADIONUCLIDE GENERATOR is any system incorporating fixed parent radionuclide from which is produced a daughter which is to be obtained by elution or by any other method and used in a radiopharmaceutical preparation.

15. RADIONUCLIDE KIT is any preparation to be reconstituted or combined with radionuclide in the final radiopharmaceutical, usually prior to its administration.

16. RADIONUCLIDE PRECURSOR is any other radionuclide produced for labeling (marking) of another substance prior to administration.

17. ESSENTIAL MEDICINAL PRODUCTS are basic medicinal products intended for treatment of the most common diseases of the majority of population and as such identified by competent authority.

18. GENERIC MEDICINAL PRODUCT is a medicinal product which has the same qualitative and quantitative composition in active substance(s) and the same medicinal product form (or the various immediate-release oral medicinal product forms) as the reference medicinal product, and whose bioequivalence with the

reference medicinal product has been demonstrated by appropriate bioavailability study. The different salts, esters, isomers, mixtures of isomers, ethers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and efficacy of medicinal products. In that case the applicant has to submit additional information which will prove the safety and/or efficiency of the different salts, esters or derivatives of the approved active substance. Bioavailability studies need not be required from the applicant if relevant proof is submitted, in accordance with the relevant European Union instructions which will justify the absence of such study.

19. REFERENCE MEDICINAL PRODUCT is medicinal product manufactured from the original or medicinal product with marketing authorization in the Republic of Macedonia or in the European Union member whose bioequivalence with the original medicinal product has been proved

20. MAGISTRAL MEDICINAL PRODUCT is any product prepared in pharmacy in accordance with a medical prescription for an individual patient.

21. GALENIC MEDICAL PRODUCT is any product prepared in a galenic pharmacy laboratory in accordance with the prescriptions of pharmacopoeia and other regulations, and is intended to be administered directly to the patients served in the concerned pharmacy.

22. HOMEOPATHIC MEDICINAL PRODUCT is any medicinal product prepared from substances or so called homeopathic ingredients in accordance with a homeopathic manufacturing procedure described by the European Pharmacopoeia, National supplement of the Ph.Eur. of the Republic of Macedonia (herein after the National Supplement) or by pharmacopoeias currently used officially in counties that have the same standards of quality of homeopathic medicinal products as the Republic of Macedonia. A homeopathic medicinal product may contain a number of principles.

23. HERBAL MEDICINAL PRODUCT is any medicinal product exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations.

24. HERBAL SUBSTANCES are mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried or sometimes a fresh form. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances. Herbal substances are precisely defined by the plant used and the botanical name according to binomial system (genus, species, variety and author).

25. HERBAL PREPARATIONS are preparations obtained by subjecting herbal substances to treatments such as extraction, distillation, squeezing, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, eteric and fatty oils, expressed juices and processed exudates

26. TRADITIONAL HERBAL MEDICINAL PRODUCTS are medicinal products which completely fulfill all of the following criteria:

- they have indications exclusively appropriate to traditional herbal medicinal products which, by virtue of their composition and purpose, are intended and designed for use without the supervision of a medicinal practitioner
- they are exclusively for administration in accordance with a specified strength and method of use
- they are an oral, external and/or inhalation preparation
- the period of traditional use, that can be proven by bibliographical or expert evidence, is at least 30 years including at least last 15 years in the Republic of Macedonia or in the European Union member countries, and
- the data on the traditional use of the medicinal product are sufficient; in particular the product proves not to be harmful in the specified conditions of use and the pharmacological effects or efficacy of the medicinal product are plausible on the basis of long-standing use and experience.

27. PHARMACOPOEIA is a list of regulations regulating manufacturing of medicinal products, control and verification of their identity, testing and establishing purity and other parameters determining quality of medicinal product and its component substances.

28. EUROPEAN PHARMACOPOEIA is a pharmacopoeia enacted based on the European Council's Convention for preparation of the European Pharmacopoeia (1964).

29. GOOD MANUFACTURING PRACTICE (GMP) is a qualitative system governing organization, surveillance and control of quality of all aspects of medicinal product manufacturing.

30. GOOD CONTROL LABORATORY PRACTICE (GcLP) is a part of good manufacturing practice related to the quality control of medicinal products.

31. GOOD LABORATORY PRACTICE (GLP) is a qualitative system governing organizational processes and conditions of planning, implementing, controlling, recording (protocol) and reporting on pre-clinical laboratory studies.

32. GOOD DISTRIBUTION PRACTICE (GDP) is a qualitative system governing the organization, implementation and control of storage of the medicinal products and medical devices according to certain order and prescribed storage conditions before further use or marketing and their transport from the manufacturer to the end user.

33. GOOD CLINICAL PRACTICE IN CLINICAL TRIALS (GCP) is an internationally recognized ethic and scientific system governing the quality of planning and implementation, recording, controlling and reporting on clinical trials on humans, and ensuring the credibility and quality of data acquired during trials and protection of rights, safety and well being of trial subjects, in accordance with the WHO Helsinki Declaration for biomedical trial on humans.

34. GOOD PHARMACEUTICAL PRACTICE (GPhP) is a set of internationally accepted standards for promotion of health by supply of medicinal products and medical devices, dissemination of information on medicines, improving patient care and prescribing in line with the method of use of the medicinal product as well as other associated activities.

35. MANUFACTURER OF MEDICINAL PRODUCTS, I.E. MEDICAL DEVICES is a legal entity authorized and responsible for manufacturing, development, quality control, packing and labeling of medicinal products or medical devices regardless of whether medicinal products or medical devices have been manufactured by themselves or by a third party on their behalf.

36. MARKETING AUTHORIZATION HOLDER is a legal person that has been granted a marketing authorization for a given medicinal product in accordance with this Law.

37. PHARMACOVIGILANCE is a system applied for the purpose of detecting, gathering, monitoring, assessing and responding to new data on safety of medicinal product and risk-benefit balance related to the use of medicinal product or its interaction with other medicinal products.

38. RISK RELATED TO THE USE OF MEDICINAL PRODUCT is any risk related to the quality, safety or efficacy of the medicinal product as regards patients' or public health, as well as any risk of undesirable effects on the environment.

39. RISK-BENEFIT BALANCE is an evaluation of positive therapeutic effects of the medicinal product in relation to the risks related to the use of the medicinal product.

40. ADVERSE REACTION TO MEDICINAL PRODUCT is any unintended and noxious response to medicinal product which occurs at proscribed usage of medicinal product.

41. SERIOUS ADVERSE REACTION TO MEDICINAL PRODUCT is any adverse reaction that results in: death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or in congenital anomaly/birth defect.

42. UNEXPECTED ADVERSE REACTION TO MEDICINAL PRODUCT is any unexpected and adverse reaction whose nature, severity and outcome are not consistent with the summary of product characteristics.

43. PERIODIC SAFETY UPDATED REPORT (PSUR) is detailed report provided by the authorization holder and is document which contains detailed data on the medicinal product safety, as well as risk-benefit balance assessment.

44. PATIENT INFORMATION LEAFLET is written information for the user which is attached to the medicinal product and contains basic information about the medicinal product and for its proper use and has to be written in a language understandable and clear for the patient-user.

45. SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) is document prepared by the manufacturer which includes basic information about the characteristics of the medicinal products and is intended for the healthcare professionals.

46. CONTACT PACKAGING OF MEDICINAL PRODUCT is the packaging which is in direct contact with the medicinal product.

47. OUTER PACKAGING OF MEDICINAL PRODUCT is the packaging in which the

contact packaging of the medicinal product is placed.

48. MARKING OF THE PACKAGING is the basic data declared on the contact and outer packaging regarding the medicinal product or medical device.

49. MEDICAL DEVICE, shall mean any instrument, apparatus, device, material and other products used in human medicine which does not achieve its principal intended action by pharmacological, immunological or metabolic means, which are used independently or in combination, including the software necessary for proper use for the purpose of:
    - diagnosis, prevention, monitoring, treatment or alleviation of disease
    - diagnosis, monitoring and supervision, treatment, alleviation or compensation for an injury or handicap
    - investigation, replacement of or modification of the anatomy or of a physiological process
    - control of conception

Medical devices shall also include:

1. materials intended by their manufacturers to be used together with a medical device to enable its use,
2. materials that have specific design characteristics and are made according to a written prescription of a qualified practitioner for the sole use of a particular patient, and
3. materials intended for clinical trials.

50. IN VITRO DIAGNOSTIC MEDICAL DEVICE shall mean medical devices that include reagents packages of reagents, reagent products, control and calibration material, instruments and apparatus, equipment or systems used independently or combined and intended for use under in vitro circumstances for testing biological specimens, including tissue specimens derived from human body, for the purpose of providing information
    - concerning physiological or pathological state
    - concerning congenital anomalies
    - determining compatibility with potential recipients, and
    - monitoring therapeutic measures

51. DOCUMENT ON CONFORMITY OF MEDICAL DEVICE is a statement on EC conformity and a certificate on EC conformity. The statement on EC conformity is issued by the manufacturer of medicinal device and it guarantees that the medical device complies with the basic requirements laid down by this Law. The EC certificate is issued either by authorized body or by Notified body in the European Unioin.

52. EC CONFORMITY MARK is mark placed on the medical device and guarantees that it fulfils all the European Union requirements for such type of devices.

53. BODY FOR ASSESSMENT OF CONFORMITY OF MEDICAL DEVICE is a legal entity, independent from manufacturer/supplier and authorized by Ministry of the Economy on the basis of a prior agreement by the Ministry of Health to assess conformity of medical devices with the basic, i.e. general and specific requirements laid down by this Law.

54. SPONSOR OF CLINICAL TRIAL is a company, institution or organization which takes responsibility for the initiation, management and/or financing of a clinical trial and

55. MATERIOVIGILANCE is a system applied for the purpose of detecting, gathering, monitoring, assessing and responding to new data on safety of medicinal product and related to the use of medical device related to possible incidents during use.

II. COMPETENT AUTHORITY

Article 3

An Agency for medicinal products shall be established for performing administrative and professional activities regarding the medicinal products and medical devices (herein after Agency) as an independent state administration authority competent for the activities in this area.

Article 4

The Agency shall be managed by a director.

The Director of the Agency shall be appointed and dismissed by the Government of the Republic of Macedonia.

The director of the agency shall be a person, who in a addition to the general conditions should also fulfill the following special conditions: university degree in the field of pharmacy and at least 5 years of work experience in the field of pharmacy.

Article 5

The competences of the Agency shall include the following:

1. issuing manufacturing authorizations for medicinal products;
2. issuing manufacturing authorizations for medical devices;
3. issuing a wholesale authorizations for wholesaling medicinal products and medical devices;
4. issuing retail authorizations for retailing medicinal products and medical devices;
5. issuing marketing authorizations for medicinal products, as well as changing and amending and renewing of the authorizations;
6. authorizing advertising of medicinal products and medical devices;
7. maintaining Register of medicinal products and Register of medical devices in the Republic of Macedonia;
8. maintaining Register of manufacturers of medicinal products and Register of manufacturers of medical devices in the Republic of Macedonia;
9. maintaining Register of entities for wholesale and Register of entities for retail sale of medicinal products and medical devices in the Republic of Macedonia;
10. issuing authorizations and/or notifications for clinical trials of medicinal products;
11. issuing authorizations and/or notifications for clinical trials of medical devices;
12. issuing import authorizations and export authorizations for medicinal products;
13. issuing certificates for compliance with the good practices principles;
14. issuing certificates for the needs of export of medicinal products and medical devices;

15. classification of products as medicinal products or medical devices;
16. establishing and maintaining farmacovigilence and materiovigilence system;
17. establishing and maintaining database;
18. inspection of the medicinal products and medical devices;
19. inspection of entities for production, wholesale and retailing;
20. activities pertaining to assure control of the quality of the medicinal products and medical devices;
21. determination of prices of medicinal products;
22. collecting and processing statistical data on the sale and consumption of medicinal products and medical devices;
23. cooperation with other institutions on promotion of rational use of medicinal products and medical devices;
24. integration into international networks of information on medicinal products and medical devices;
25. undertaking other activities pertaining to medicinal products or medical devices in accordance with this Law.

Article 6

The Minister of Health, based on the criteria stipulated in article 50 of this Law, shall authorize the accredited laboratories for analytical investigation and control of the medicinal products.

Article 7

In order to get the opinion in the procedure for marketing of a medicinal product i.e. medical device, the following standing professional and advisory committees shall be established within the Agency:
- Medicinal Products Committee;
- Traditional Herbal Medicinal Products and homeopathic medicinal products Committee;
- Clinical Trials Committee for medicinal products and medical devices;

Ad hoc committees shall be established for any expert activity for addressing specific issues.

The standing and ad hoc committees shall work according to Rules of Procedures.

The committees shall be professionally independent and autonomous within the scope of their work.

The Agency shall cover the expenses of the standing and ad hoc committees.

Article 8

The Minister of Health, shall appoint the members of the standing and ad hoc committees, from the pool of the distinguished experts and scientists in the field of medicine, dentistry, pharmacy and other fields with at least 10 year working experience in the relevant field.
The members of the standing and ad-hoc committees shall be appointed upon proposal by the Director of the Agency, upon public call.
The members of the standing and ad hoc committees are obligated to perform their activities in conscious and honest way, and they shall sign a statement on classified information and absence of conflict of interests.

Article 9

The Minister of Health shall, upon proposal by the Director of the Agency, if necessary, engage experts for the assessment of medicinal products and medical devices.

The persons stipulated in paragraph 1 of this article shall be obligated to sign a statement on confidentiality and absence of conflict of interest.

The Agency shall cover the expenses of the external experts and scientists.

III MEDICINAL PRODUCTS

Article 10

The Law regulates medicinal products for human use intended to be placed on the market or to be exported, either prepared industrially or manufactured by a method involving an industrial process.

The provisions of this Law shall also apply to products defined by other laws if, in accordance to their characteristics they can be defined as medicinal product in accordance with this Law.

Article 11

Medicinal product can be on the market provided that:
- marketing authorization has been issued pursuant to the procedures prescribed by this Law;
- is labeled and has patient information leaflet pursuant to the marketing authorization;
- import authorization was issued pursuant to this Law;
- quality control of medicinal products has been performed in line with the Law; and
- medicinal product is used for preclinical or clinical trials providing that notification or authorization of clinical trial was issued.

By way of exception of paragraph 1 of this article, medicinal product, without marketing authorization, can be available on the basis of compassionate use e.g. for compassionate reasons to a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life threatening and who can not be treated satisfactorily by other authorized medicinal product. The medicinal product stipulated in paragraph 2 of this article must either be subject of a procedure for marketing authorization or must be undergoing clinical trial.

Article 12

It is prohibited to market products presented as having properties for preventing or treating of diseases or conditions as described in definition of medicinal products if they are not classified as medicinal products in accordance with this Law

Article 13

According to the method and place of dispensing, medicinal products shall be classified into

- medicinal products that are dispensed only on prescription in pharmacies
- medicinal products not subject to prescription dispensed (over the counter, OTC) in pharmacies
- medicinal products used only in medical institutions.

Medicinal products dispensed over the counter are with a wide range of therapeutic indications, of a small toxicity, with small overdose possibility, minimal interactions and with indications well known to patients and appropriate to be used for self-medication.

Method of prescribing Medicinal products shall be defined in the procedure marketing authorization of medicinal product.

The Minister of health shall determine in greater detail the conditions for the manner of prescribing and dispensing of the medicinal products.

Article 14

If medicinal product, already classified to be dispensed only on prescription, on the basis of submitted relevant results from preclinical tests or clinical trials may be reclassified to be dispensed over the counter.

The Agency cannot, for the purpose of evaluation other applicant's application, refer to the results of the submitted preclinical and trials within one year form the authorization of the reclassification,

Article 15

Marketing authorization holder is responsible for placing the medicinal products on the market and for any damage caused by quality defect or by proper use of medicinal product.

Marketing authorization holder and medical professionals are not responsible for consequences of treatment that was not in line with issued marketing authorization or for consequences of treatment with medicinal product without marketing authorization if the treatment was recommended or requested by the Agency or Ministry of health in cases of exceptional situations concerning public health protection.

Marketing authorization holder together with wholesaler of medicinal products have public service obligation i.e. guarantee permanently an adequate range and quantity of medicinal products in a relatively short period of time to meet requirements for supply with the medicinal product.

Article 16

Medicinal products marketed in the Republic of Macedonia must be manufactured and controlled according to the methods and requirements of the European Pharmacopoeia and the national supplement.

Should in the European pharmacopoeia and in the national supplement thereof not prescribe

methods of manufacture and requirements concerning quality, medicinal products have to be manufactured and controlled according to methods and requirements of other acknowledged pharmacopoeias or according to the methods proposed by the manufacturer.

III.1 MARKETING AUTHORIZATION OF MEDICINAL PRODUCT

Article 17

Medicinal product can be placed on the market if a marketing authorization has been issued in accordance with this law.

A marketing authorization shall not be required for:
- medicinal products subject to clinical trial
- medicinal products intended for continuation of treatment started abroad
- products intended to be further processed
- medicinal products to be used for research and development
- magistral preparations
- galenic products
- radiopharmaceuticals prepared at the time of use by a person or by a healthcare institution authorized to use such a medicinal products
- blood and blood components
- medicinal products for which import license has been granted on the basis of Art.79 of the Law, and
- medicinal products provided as a donation according this Law

Article 18

Application for authorization for marketing authorization procedure (hereinafter: the application) shall be submitted to the Agency.

The application stipulated in paragraph 1 of this article may be submitted by:
- manufacturers of medicinal products with a registered office in the Republic of Macedonia
- legal representatives of foreign manufacturers with a registered office in the Republic of Macedonia provided that they have concluded an agency agreement stipulating their valid insurance covers territory of the Republic of Macedonia
- branches of foreign manufacturers with registered office in the Republic of Macedonia stipulating their valid insurance covers territory of the Republic of Macedonia and
- trade representation office of foreign manufacturer with registered headquarters in the Republic of Macedonia, if their valid insurance covers the territory of the Republic of Macedonia

Article 19

Applicant will be a marketing authorization holder (hereinafter authorization holder).

Marketing authorization holder shall be responsible for placing medicinal product on the market.

Marketing authorization holder shall be obliged to establish and maintain a system of pharmacovigilance and to designate a person responsible for pharmacovigilance who is

permanently and continuously available.

The person stipulated in paragraph 3 of this article must have university degree in human medicine or pharmacy.

Article 20

The application stipulated in article 18 of this Law shall include the following components:

1. administrative component of documentation containing:
   - information on the medicinal product and issued marketing authorizations
   - information on manufacturer, information on production sites, manufacturing authorization based on fulfilling requirements of good manufacturing practice and GMP certificate not older than 3 years;
   - information on future marketing authorization holder for the medicinal product
   - proposed summary of product characteristics
   - proposed patient information leaflet
   - proposed packaging (contact and/or outer),
   - Certificate of Pharmaceutical Product
   - list of countries that have already authorized marketing of the medicinal product and list of countries in which the application was submitted, rejected or withdrawn
   - expert opinions on documentation concerning quality, safety and efficacy of the medicinal product that represent a constituent part of submitted documentation together with information on the experts

2. Analytical i.e. pharmacological-chemical and biological component of documentation containing information on active substance quality and medicinal product quality: qualitative and quantitative particulars of the medicinal product, description of manufacturing methods, quality control of the raw materials, manufacturing quality control, final product quality control, stability study and other information on quality of medicinal product relevant for the health protection and environment.
3. Pharmacological-toxicological component of documentation containing information on pharmacodynamic and pharmacokinetic properties of medicinal product, its toxicity and effects on the reproductive function, data on embryo-fetal toxicity, mutagenic and carcinogenic potential, data on local tolerance and other data necessary for public health protection and
4. Clinical component of documentation containing general information on clinical trials, manner of their conduct, compliance with ethical requirements, their results, clinical pharmacological data, data on biological availability and bioequivalence (if applicable), data on clinical safety and efficacy, information on exceptional circumstances in trials (if applicable) and data on experience following the authorization in other countries

Article 21

The applicant is responsible for the authenticity of the submitted data

Documentation enclosed in the application for authorization of medicinal product is in the property of the applicant, is archived with the Agency and considered is classified with the exception of summary of product characteristics, patient information leaflet and the packaging data for which information can be provided to the professional public for appropriate and rational application of the medicinal product.

Article 22

As an exception of the provisions of Article 20, applicants shall not be required to provide its own results of pharmacological tests or clinical trials if they can demonstrate:

1. that bibliographic data on pharmacological-toxicological tests and clinical trials are taken over from published scientific literature and contain all information required in Article 20 paragraph 1, items 3 and 4 of this Law, provided that the substance in the medicinal product is well established, the product particulars are well known and its efficacy proven and that the active substance has been used as a medicinal product for at least ten years in the Republic of Macedonia or in any European Union and for which the published scientific data are coherent and sufficient and enable the extrapolation from the substance to the medicinal product for which a marketing authorization is required or

2. that medicinal product concerned is a generic of a reference medicinal product that has already been authorized for at least eight years (exclusivity of data) in the Republic of Macedonia or European Union, provided that the Agency may issue a marketing authorization only after the lapse of at least ten years (market exclusivity) from the issuance of the marketing authorization of the reference product. The ten years period can be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies

Since different salts, esters, isomers, mixtures of isomers, ethers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and efficacy of medicinal products, in that cases the additional information on providing proof of the safety and/or efficacy of the various salts, esters or derivatives of an authorized active substance must be supplied by the applicant. The various immediate release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form. Bioavailability studies need not be required of the applicant if he can demonstrate that the generic medicinal product meets the relevant criteria as defined in the appropriate scientific guidelines

Article 23

In case where the medicinal product does not fall within the definition of generic medicinal product or where the bioequivalence cannot be demonstrated through bioavailability studies or in case of changes in the therapeutic indications, strength, pharmaceutical form or route of administration, vis-a-vis the reference medicinal product the results of appropriate pre-clinical tests or clinical trials have to be provided by the applicant.

Article 24

When the biological medicinal product which is similar to a reference biological product does not meet the condition in the definition of generic medicinal product, owing to, in particular differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided. The type and quantity of supplementary data to be provided must comply with the relevant criteria.

Article 25

If an application is made for a new indication for a well established substance, a non cumulative period of one year of data exclusivity shall be granted, provided that significant pre-clinical and clinical studies were carried out in relation to the new indication.

Article 26

Conducting the necessary studies and trials with a view to application of articles 22 paragraph 1 under 2, articles 23 and 24 of the Law, and the consequential practical requirements in accordance to this Law shall not be regarded as breech of patent rights or to supplementary protection certificate rights.

Article 27

In the case of medicinal product containing active substance used in the composition of authorized medicinal products but not hitherto used in fixed combination for therapeutic purposes, the results of new pre-clinical tests or new clinical trials relating to that combination shall be provided in accordance with Article 20 but it shall not be necessary to provide scientific references relating to each individual active substance

Article 28

Following the granting of a marketing authorization, the marketing authorization holder may allow use to be made of the pharmaceutical, pre-clinical and clinical part of the documentation contained in the file of the medicinal product, with a view to examine subsequent applications relating to other medicinal products possessing the same qualitative and quantitative composition and the same pharmaceutical form.

Article 29

The application for medicinal product marketing authorization shall be submitted for every pharmaceutical form, strength and size of packaging of the medicinal product.

The Agency shall approve or reject the application within not more than 210 days from the receipt of a complete application for a marketing authorization, based on the documentation submitted and proposal of the Medicinal Products Committee of the product quality, safety and efficacy of the medicinal product.

As an exemption from paragraph 2 of this article, when an application is filed for a medicinal product that has a marketing authorization in at least three European Union member states, the Agency shall approve the application within a time period not exceeding 15 days from the day from the receipt of a complete application for a marketing authorization, based on the documentation submitted, quality, safety and efficacy of the medicinal product obtained in the procedure for marketing authorization in the European Union and upon a proposal from the Committee for Medicinal Products.

As an exemption from paragraph 2 of this article, when an application is filed for a medicinal product that has a marketing authorization in less than three European Union member states, the Agency shall approve the application within a time period not exceeding 90 days from the day from the receipt of a complete application for a marketing authorization, based on the documentation submitted, quality, safety and efficacy of the medicinal product

obtained in the procedure for marketing authorization in the European Union and upon a proposal from the Committee for Medicinal Products.

As an exemption from paragraph 2 of this article, when an application is filed for a medicinal product that has a marketing authorization in USA, Japan, Switzerland and Canada, the Agency shall approve the application within a time period not exceeding 60 days from the day from the receipt of a complete application for a marketing authorization, based on the documentation submitted, quality, safety and efficacy of the medicinal product obtained in the procedure for marketing authorization in the USA, Japan, Switzerland and Canada and upon a proposal from the Committee for Medicinal Products.

If the Agency does not respond in writing to the application for marketing authorization of the medicinal product within the specified time period stipulated in 2, 3, 4, and 5 of this Article, it shall be considered that the response is positive and shall have the same legal effect as if the marketing approval for medicinal product has been obtained.

Article 30

The marketing authorization shall be issued for the period of eight years.

The marketing authorization holder is obligated to inform the Agency for the day of commencement of the marketing of the medicinal product.

The Agency shall reject issuing a marketing authorization should the assessment of the provided documents demonstrate the following occurrences:
- that the risk-benefit ratio is unfavorable
- that the product quality, safety and or efficacy are unsubstantiated or insufficiently substantiated
- that the qualitative or quantitative particulars of the medicinal product are inconsistent with the information provided in the documentation
- that the documentation, labeling or patients information leaflet is inconsistent with this Law and
- if certain data or information in the application in not correct

Article 31

As an exemption of the provisions of paragraph 1 and 2, item 2 of article 30 of this Law, the Agency, in the exceptional cases of objective and justifiable reasons concerning public health (rare diseases, ethical aspects and life threatening diseases), if an appropriate medicinal product is unavailable, may issue conditional marketing authorization for the period until the cease of the circumstances but not longer than 1 year.

Article 32

Constituent part of a marketing authorization shall be approved summary of product characteristics, patient information leaflet and packaging.
Summary of product characteristics from the paragraph 1 of this Article shall contain at least the basic information on the medicinal product: name, common name, qualitative and quantitative particulars, pharmaceutical form, strength, size of packaging, marketing authorization holder, dosage, method of administration, indications, contraindications, precautions, dispensing regime, adverse reactions, duration of the treatment, storage conditions and other required information. The document is aimed to inform health care professionals.

Patient information leaflet and packaging from the paragraph 1 of this Article shall contain all necessary data in line with Article 84 and 85 of the Law.

Article 33

Contents of the application, the procedure and the requirements for obtaining a marketing authorization, the form and contents of the required documentation and conditions for recognition of marketing authorization issued in the European Union member states, the manner for obtaining a conditional marketing authorization as well as fees to be paid shall be prescribed in greater details by Minister of health

Article 34

A marketing authorization shall cease to be valid:

1. if the time for which it has been issued has expired

2. the Agency revokes the marketing authorization upon request the marketing authorization holder with justification and

3. the Agency may revoke, withdraw or vary the marketing authorization provided that:

- the medicinal product has been marketed contrary to the marketing authorization
- the medicinal product has been marketed contrary to this Law
- the medicinal product is harmful under the prescribed conditions for use;
- the medicinal product does not have favorable risk-benefit ratio under prescribed conditions of use;
- the medicinal products lacks therapeutic efficacy e.g. its therapeutics efficacy is not sufficient for achieving therapeutic results
- the medicinal product has qualitative and/or quantitative particulars that are inconsistent with those declared in marketing authorization;
- the medicinal product has not been placed on the market within three (3) years from the issuance of its marketing authorization, unless so approved by the Agency on the basis of a substantiated request of the marketing authorization holder, and
- if any particulars supporting the marketing authorization are incorrect or have not been amended according the provisions of the Law or controls have not been carried out according the provisions of the Law.

Article 35

A medicinal product whose marketing authorization has expired and has not been renewed within the time period determined by this Law may be marketed by the date of expiry but not longer that eighteen months from the expiry of the authorization, except in cases related to medicinal product safety or efficacy.

Article 36

Should the manufacturer decide to cease manufacturing or marketing of a medicinal product before the expiry of the marketing authorization, he/she is obligated to report it to the Agency at least two months before ceasing manufacturing or marketing of the medicinal product.

Article 37

The marketing authorization may be renewed before the expiration of the time period on the basis of re-evaluation of the risk-benefit ratio by the Agency.

For the purpose of renewal of marketing authorization, the marketing authorization holder shall submit the application to the Agency at least six month before the marketing authorization ceases to be valid. The application shall contain a updated version of the file in respect of quality, safety and efficacy, including all variations introduced since the marketing authorization was granted. The documentation shall include updated administrative information, information on periodical safety updated reports, additional information on medicinal product quality, safety and efficacy, if needed, chronological list of approved variations as well as other information required for re-evaluating the risk-benefit balance.

Within not more than sixty days from the receipt of a complete application for a marketing authorization revewal, the Agency shall decide to approve or to reject the requested renewal of marketing authorization based on the documentation submitted and Medicinal Products Committee's proposal on the product's risk-benefit ratio.

The time limit referred in paragraph 3 of this article shall be suspended on the day when the Agency requests the applicant to provide additional documents, information or explanations that are considered necessary, and this suspension shall last until the request of the Agency has been met.

The renewed, the marketing authorization shall be valid for an unlimited period of time, unless the Agency, on justified grounds related to pharmacovigilance, decides to proceed with one additional five-year renewal.

Minister of health shall prescribe the manner of the renewal of a marketing authorization, form and contents of the required documentation as well as fees to be paid.

Article 38

The marketing authorization holder shall follow all scientific and technical developments related to the authorized medicinal product, shall take into account findings concerning product's quality, safety and efficacy and if necessary introduce any changes necessary for manufacture or control of medicinal product according to state of the art science and technology.

All changes or other information which cause variation of the marketing authorization or change of its marketing authorization documentation shall be submitted to the Agency.

Article 39

The marketing authorization holder shall regularly notify the Agency of all smaller changes (types IA and IB) in the procedure for marketing authorization, introducing the changes only if the Agency fails to give a negative opinion on them within thirty days from the day of notification and all the necessary documents concerning the change.

Article 40

To introduce major changes of type II in the marketing procedure, the marketing authorization holder shall be obliged to file an application with the Agency without delay.

The Agency shall decide on the application for introducing major changes within sixty days from the day of receipt of a complete application.

The time limit of paragraph 2 of this article shall be suspended on the day when the Agency requests the applicant to provide additional information or explanations that are considered necessary and this suspension of the time limit calculation shall last until the request of the Agency has been met.

Article 41

The marketing authorization holder may submit an application in the case of extension of the existing application to changes that concern active substance, pharmaceutical form, strength or new indication field, provided that the reference to the already submitted parts of documentation which is accepted.

The procedure for extension of the application stipulated in paragraph 1 of this article is as for a new marketing authorization.

Article 42

Minister of health shall prescribe the form and the content of application/notification and the manner of notification or approval of the changes of marketing authorization or already provided documentation stipulated in article 39 and 40 paragraph 1 of this Law, as well as the fees that have to be paid.

Article 43

The application for registration of traditional herbal medicinal products shall contain the following documentation:
1. administrative component of documentation according to Art 20 paragraph 1 item 1 of the Law
2. pharmaceutical-chemical-biological documentation according to Art 20 paragraph 1 item 2 of this Law
3. bibliographic or experts evidence for the effect of the medicinal product in question, or a similar medicinal product has been in medicinal use through a period of at least 30 years including at least 15 years in the Republic of Macedonia or in the European Union and
4. a bibliographic review of safety data together with an expert report, and where required by the Agency, upon additional request, data necessary for assessing the safety of the medicinal product.

Contents of the application, the manner of registration for traditional herbal medicinal products and the form, contents of the required documentation and conditions for recognition of marketing authorization issued in the European Unionas well as fees to be paid shall be prescribed by the Minister of health

Article 44

The Agency shall reject issuing a marketing authorization for traditional herbal medicinal product should the assessment of the provided documents demonstrate the following occurrences:
- that therapeutic indications are not proved according to this Law;
- that the qualitative and/or quantitative composition of the medicinal product is not as declared
- that the traditional herbal medicinal product could be harmful under normal conditions of use
- that the data on traditional use are insufficient, especially if pharmacological effects or efficacy are not plausible on the basis of long-standing use and experience
- that pharmaceutical quality is not satisfactorily demonstrated.

Article 45

The application for registration of homeopathic medicinal products shall be submitted provided that the medicinal products:

1. are administered orally or externally
2. no specific therapeutic indication appears on the packaging of the medicinal product or in any information relating thereto, and
3. there is a sufficient degree of dilution to guarantee the safety of the medicinal product; in particular, the medicinal product may not contain either more than one part per 10 000 of the basic tincture or more than 1/100 of the smallest dose used in allopathy with regard to active substances whose presence in an allopathic medicinal product results in the obligation to submit a prescription.

Contents of the application, the procedure and manner of registration for homeopathic medicinal products, the form and contents of the required documentation, conditions for advertising and labeling of the products, conditions for recognition of marketing authorization issued in the European Union member states as well as fees to be paid shall be prescribed by the Minister of health

Article 46

List of medicinal products for which the marketing authorization was issued and list of medicinal products for which the marketing authorization was rejected, changed, withdrawn, shall be published in the Official Gazette of the Republic of Macedonia, at least twice a year.

Article 47

Marketing authorization holder can transfer the marketing authorization for medicinal product to another holder provided that the latest fulfils criteria for marketing authorization holder prescribed by the Law and accepts obligations and rights of marketing authorization holder for the medicinal product in question.

The Minister of health shall prescribe the manner of transfer of marketing authorization, content of documentation to be submitted and other requested data for transfer of the marketing authorization as well as fees to be paid.

Article 48

The Minister of Health shall determine the amount of the fees stipulated in articles 33, 37 paragraph 6, 43 paragraph 2, 45 paragraph 2 and 47 paragraph 2 of this Law, which have to be paid by the applicant depending on the type of procedure and the depending on:

- the type of tests which need to be done,
- the real administrative and material expenses,
- the professional assessment of the documentation,
- the activity of the standing and ad-hoc committees.

III.2 TESTING AND TRIALS OF MEDICINAL PRODUCTS

Article 49

Prior to being placed on the market, a medicinal product must undergo analytical (pharmaceutical-chemical-biological), pharmacological-toxicological tests and clinical trials in order to confirm its quality, safety and efficacy.

A medicinal product may undergo analytical (pharmaceutical-chemical-biological), pharmacological-toxicological tests and clinical trials even if it has been granted a marketing authorization, with the purpose of obtaining additional information on the medicinal product or its control.

Analytical (pharmaceutical-chemical-biological), pharmacological-toxicological tests and clinical trials shall be performed in accordance with good manufacturing practice /good control laboratory practice, good laboratory practice and good clinical practice in clinical trials.

Minister of health will publish guidelines for the principles of good manufacturing practice including a good control laboratory practice, good laboratory practice and good clinical practice in clinical trials

Article 50

Analytical, pharmacological-toxicological tests and clinical trials may only be carried out by legal persons that meet the requirements pertaining to premises, equipment and staff, as well as the principles of good practices and if they are authorized by Minister of health for those activities.

Data on analytical and pharmacological-toxicological tests and clinical trials are integral parts of documentation submitted for the purpose of obtaining marketing authorization of medicinal product. The tests have to comply with the state of the art science and technology and principles of good practices and have to be described in details and in a way that tests and trials can be repeated and results compared.

Minister of health shall authorize the legal entitles stipulated in paragraph 1 of this article for investigation of medicinal products and shall provide the fees to be paid.

Article 51

Analytical tests of medicinal products is pharmaceutical-chemical-biological-microbiological testing of medicinal product's quality and shall be carried out in accordance with the principles of good control laboratory practice, with the data included in the documentation that supports application for a marketing authorization and with information defined in specifications for the medicinal product concerned.

Minister of health shall describe in detail manner and procedures for analytical testing of medicinal products.

Article 52

Pharmacological-toxicological, i.e. pre-clinical tests of medicinal products is a procedure for evaluating the safety of medicinal products and shall be carried out in compliance with principles of good laboratory practice.

The procedure of carrying out pharmacological-toxicological tests, described in the documents provided to obtain a marketing authorization, must determine pharmacodynamic, pharmacokinetic and toxicological characteristics of medicinal products, which have been observed on lab animals, and foresee their possible effects on human beings. The results of pharmacological-toxicological tests must include the results of all available tests of a medicinal product, regardless of whether favorable or unfavorable.

Minister of health shall prescribe manner and procedures for pharmacological-toxicological testing of medicinal products.

Article 53

Clinical trials of medicinal products are trials of medicinal products that are carried out on healthy volunteers and/or patients for the purpose of discovering or confirming clinical, pharmacological, pharmacodynamic or pharmacokinetic effects of investigational medicinal products, identifying their undesirable effects or studying their absorption, distribution, metabolism and excretion in order to verify medicinal product safety and efficacy. Clinical trials include bioequivalence studies, i.e. bioavailability tests.

Article 54

Clinical trials of medicinal products shall be carried out only if the provided results of analytical, pharmacological-toxicological tests have been submitted and if trials are performed on medicinal product that does not influence the human genetic code line and if the danger posed by the use of the medicinal product does not exceed the health rationale of the trial.

Clinical trials of medicinal products shall be performed in accordance with ethical principles of the Declaration of Helsinki and other signed international agreements, in accordance with principles of good clinical practice in clinical trials and in accordance with mandatory and guaranteed protection of personal data and rights of persons involved in the trials (hereinafter test subjects).

Article 55

The test subjects must be informed on all relevant details on the trials, about the purpose of the trial, its nature, the procedure and the potential risk involved, in a way understandable to them and in writing.

The clinical trial of the medicinal product may be performed only if the test subject gives written consent.

The consent stipulated in paragraph 2 of this article may be revoked at any time.

Article 56

Clinical trials that are part of documentation that supports application for a marketing authorization, shall contain the clinical trials results that are sufficiently specified and objective to allow objective assessment of the risk-benefit balance for a patient and of medicinal product safety and efficacy, as well as an opinion on whether a medicinal product meets the requirements for a marketing authorization.

Article 57

The application for clinical trials may be submitted by the manufacturer, the sponsor of the trial or his authorized representative.

The applicant for a clinical trial of a medicinal product is responsible for the implementation of the trial and for the course of the clinical trial and is obligated to submit a report to the Agency, every three months i.e. to submit final report for the results of the clinical trial of the medicinal product, within one year from the day of conclusion of the clinical trial of the medicinal product.

The applicant for a clinical trial of a medicinal product must, prior to the commencement of the trial, to insure the test subjects for any possible damage resulting from the trial of the medicinal product in accordance with the general regulations for insurance of damage.

Article 58

The applicant for a clinical trial of a medicinal product that has not yet received a marketing authorization in the Republic of Macedonia, new indication, new target group, new application method or new dosage shall file an application with the Agency prior to the clinical trial.

The application for clinical trials shall contain summary of information on quality of the medicinal product, all necessary information on results of pre-clinical tests or safety of the product and results of clinical trials already performed on the investigational medicinal product, protocol of the proposed trial, positive opinion of the Ethical Committee, information on investigational institution, investigators and other information necessary for decision on the approval or rejection of the trial.

The Minister of Health shall establish the Ethical Committee stipulated in paragraph 2 of this article.

The Agency shall decide to approve or to reject the clinical trial authorization within not more than sixty days from the day of receipt of a complete application for the clinical trial on the

basis of the opinion of the Committee for Clinical Trials.

The time limit stipulated in paragraph 3 of this article shall be suspended on the day when the Agency requests the clinical trial applicant to provide additional information or explanations that are considered necessary and this suspension of the time limit calculation shall last until the request of the Agency has been met.

Article 59

The applicant for a clinical trial of a medicinal product that has already been issued a marketing authorization in the R of Macedonia and for bioequivalence studies shall notify the clinical trial with the Agency prior to the commencement of the clinical trail.

The notification for clinical trails shall contain information about the medicinal product, information on quality of the medicinal product and results of pre-clinical tests or safety of the product and results of clinical trials already performed on the investigational medicinal product, the trail protocol, positive opinion of the National ethic committee information on investigational institution, investigators and other information necessary for decision on the approval or rejection of the trial

The Agency shall, within not more than thirty days from the day of receipt of a complete notification for clinical trial inform the applicant of the reasons for rejecting the clinical trial.

The time period stipulated in paragraph 3 of this article shall be suspended on the day when the Agency requests the clinical trial applicant to provide additional information or explanations that are considered necessary and this suspension of the time limit calculation shall last until the request of the Agency has been met.

If the clinical trial applicant does not receive a negative response from the Agency within thirty days, it may commence the clinical trial.

Article 60

The manufacturer i.e. the sponsor must notify with the Agency all relevant changes of the clinical trials.

If the manufacturer i.e. sponsor does not receive a negative response from the Agency within thirty days, it may introduce the change.

Article 61

In case of unexpected serious adverse reaction or event occurred during a clinical trial, the manufacturer i.e. the sponsor shall immediately inform the Agency, the ethics committee and legal person from the article 87 paragraph 2 of this Law.

Article 62

The Agency shall supervise the conduct of clinical trials in accordance with this Law, and principles for good clinical practice in clinical trials

Article 63

The Agency may request a temporary or permanent suspension of a clinical trial of a medicinal product, for the purpose of protecting public health.

Article 64

Minister of health shall prescribe the manner and the procedure for clinical trials, content of documentation as well as fees to be paid.

III.3 MANUFACTURING OF MEDICINAL PRODUCTS

Article 65

Legal entities may manufacture medicinal products only after they have been granted a manufacturing license.

Manufacturing license also allows the sale of the manufactured medicinal product from manufacturer to wholesalers.

Manufacturing license shall be issued for:
- manufacturing process as a whole or parts of manufacturing process
- particular production site
- particular pharmaceutical form
- manufacturing of active substance and
- manufacturing of excipients

Manufacturing license shall be required notwithstanding that the medicinal products manufactured are intended for export or for clinical trials.

Manufacturing license is also required for performing activities that include placing stickers, inserting patient information leaflet etc. as parts of the manufacturing process.

Article 66

Manufacturer of medicinal products derived from human blood must ensure that collecting, treating or processing blood, its components and derivatives as raw material must comply with conditions determined by a law.

Manufacturer of radiopharmaceutical preparations must ensure that that raw material for the products comply with conditions regulated by this law

Article 67

The manufacture of galenic preparations produced in galenic laboratory of an authorized pharmacy up to 100 finished packages per day shall not be considered manufacture of medicinal products under this Law.

Minister of Health shall prescribe the conditions regarding the space, equipment and staff that have to be fulfilled by the legal entities who manufacture galenic medicinal products.

Article 68

The legal entity that manufactures medicinal products shall meet the following requirements:

- to have appropriate premises, equipment and staff for manufacturing, in accordance with the scope of demands of the manufacture, control, storage and transport the medicinal products in line with principles of good manufacturing practice
- given the volume and complexity of their medicinal product manufacture, to employ an adequate number of professionals holding university degree in pharmacy, chemistry, technology, medicine, dentistry or other suitable profile and with an additional appropriate education concerning the manufacture concerned.
- to have employed a person responsible for manufacturing of individual medicinal product batches, who has an university degree in pharmacy and specialization in pharmaceutical technology and is always at disposal and shall guarantee that each batch of the medicinal product is manufactured in compliance with the Law and the requirements of marketing authorization.
- to have employed a person responsible for quality control of individual medicinal product batches, who has an university degree in pharmacy and specialization in testing and control of medicinal products and is always at disposal and shall guarantee that each batch of the medicinal product is controlled in compliance with the Law and the requirements of marketing authorization.
- to have employed a person responsible for manufacturing of individual medicinal product batches, who has an university degree in pharmacy and additional knowledge in manufacturing and control of medicinal products and is always at disposal and shall guarantee that each batch of the medicinal product is manufactured and controlled in compliance with the Law and the requirements of marketing authorization.
- manufacturing process must be performed in line with principles and guidelines of good manufacturing practice
- raw materials used as active substances or excipients shall be produced in line with the principles of good manufacturing practice.
- to manufacture only those medicinal products covered by the granted manufacturing authorization and in compliance with granted marketing authorization for the medicinal products and
- to introduce a quality system in accordance with the principles of good manufacturing practice

Article 69

The application for manufacturing license shall be submitted to the Agency.

The application stipulated in paragraph 1 of this article shall include proves that the conditions stipulated in article 68 of this Law are met.

The Agency shall within ninety days from the day of receipt of complete application, approve or reject the application for manufacturing license on the basis of submitted documentation and results of the inspection of GMP performed.

The time limit stipulated in paragraph 3 of this article shall be suspended on the day when the Agency requests the applicant to provide additional documentation or data that are considered necessary and this suspension of the time limit calculation shall last until the request of the Agency has been met.

Manufacturing license shall be issued without a time limit.

Article 70

The manufacturer shall notify the Agency about any changes concerning the conditions defined in Article 68 of this Law.

The Agency shall, within not more than thirty days from the receipt of a complete notification approve or reject the change. This period shall be prolonged to 90 days if the change requires GMP inspection of the production site.

The time limits stipulated in paragraph 2 of this article shall be suspended on the day when the Agency requests the applicant to provide additional documentation or data that are considered necessary and this suspension of the time limit calculation shall last until the request of the Agency has been met.

Article 71

Manufacturer shall be subject to regular inspection or inspection upon request of the Agency.

Manufacturer shall enable regular and ad hoc inspections performed by inspectors according to the Law.

The manufacturer shall inform the Agency about any major incidents or mistakes in manufacturing process or other situations that might concern public health.

Manufacturing license shall be suspended or revoked should the Agency that the manufacturer of medicinal products no longer satisfies the requirements determined in the Law.

Contents of the application, the documentation and the details regarding space, equipment, staff for obtaining a manufacturing license, as well as fees to be paid shall be prescribed by the Minister of health

III.4 MARKETING OF MEDICINAL PRODUCTS

Article 72

Marketing of medicinal products include import, export, wholesale and retail of medicinal products

Legal entities performing marketing of medicinal products and marketing authorization holders shall, on request of the Agency, are obligated to provide the data on the amount of sale and other necessary data concerning the sale.

Article 73

Wholesale of medicinal product shall include purchase, storage transport, distribution and sale of medicinal product.

Wholesale distribution of medicinal product may only be carried out by legal persons holding

a license for wholesale medicinal products issued by the Agency (herein after wholesaler).

Wholesalers shall be allowed to purchase medicinal products from legal persons that hold the license for manufacturing or wholesale distribution of medicinal products and to sell medicinal products to legal persons that hold the license for wholesale or retail sale of medicinal products, as well as to healthcare institutions.

The manufacturer can directly supply medicinal products from its own production program to healthcare institutions with the exception of pharmacies if it fulfills the wholesale conditions.

Wholesalers are obligated to purchase, sell or distribute medicinal products for which a marketing authorization or import authorization was granted or investigational medicinal products for approved or notified clinical trials as well as medicinal product designed for further manufacturing only between each other, without cumulating the determined wholesale fee.

The wholesalers must not perform retail sale without the retail sale.

Article 74

Legal entity dealing in the wholesale of medicinal products shall meet the following requirements:
- to have at appropriate premises, equipment and staff for wholesale, transport, distribution and storage corresponding to the quantity and type of medicinal products that are subject to wholesale;
- to have employed an adequate number of professionals holding university degree in pharmacy and other suitable profiles;
- to have employed a person responsible for receiving, storage, distribution, transport and dispensing the medicinal products as well as reviewing the documentation that ensures traceability of medicinal products. This responsible person shall hold university degree in pharmacy and shall be permanently at disposal.
- to keep appropriate documentation in a manner that enables traceability of medicinal products and the immediate withdrawal of a medicinal product from the market and to monitor complaints;
- to meet requirements for performing trade activities in line with legislation on trade;
- to have introduced quality system and organized work processes according to the principles of good distribution practice; and
- to meet a products public service obligation e.g. obligation to guarantee permanently and adequate range of medicinal products to meet requirements on the territory of the Republic of Macedonia and to deliver the supplies requested within a very short period of time to the end users.

Article 75

Wholesaler dealing with import of medicinal products (hereinafter: importer) shall in addition to the requirements listed in art 74 have accredited laboratories with appropriate facilities, equipment and staff for performing control of imported batches of medicinal products including a requirement to have employed or otherwise contracted a qualified person who has an university degree in pharmacy and specialization in medicinal products testing and control who is always at disposal and shall guarantee that each batch of the imported medicinal product is subject of control in compliance with this Law and the requirements of marketing authorization or import authorization.

As an exemption of the provision of the previous paragraph, importer may enter into an agreement Official Medical Control Laboratory to provide the above mentioned control on their behalf.

Importers that perform parts of manufacturing process (e.g. placing stickers, inserting patient information leaflet etc.) must have in addition to wholesale license, a manufacturing license for the processes performed.

Article 76

The application for wholesale license shall contain proof of fulfilling conditions defined in Article 74 and shall be submitted to the Agency

The Agency shall within ninety days from the day of receipt of complete application, approve or reject the application for wholesale license on the basis of submitted documentation and results of the inspection of the conditions stipulated in article 74 of this Law.

The time limit stipulated in paragraph 2 of this article shall be suspended on the day when the Agency requests the applicant to provide additional documentation or data that are considered necessary and this suspension of the time limit calculation shall last until the request of the Agency has been met.

Wholesale license shall be issued without a time limit.

Article 77

The wholesaler shall notify the Agency about any changes concerning the conditions defined in Article 74 on the basis of which the wholesale license has been granted.

The Agency shall, within not more than thirty days from the receipt of a complete notification approve or reject the change. This period shall be prolonged to 90 days if the change requires inspection of the wholesale site

The time limit stipulated in paragraph 2 of this article shall be suspended on the day when the Agency requests the clinical trial applicant to provide additional documentation or data that are considered necessary and this suspension of the time limit calculation shall last until the request of the Agency has been met.

Article 78

Wholesaler shall be obligated to enable inspection in accordance with this Law.

Wholesaler shall inform the Agency about any incidents or mistakes in the work process or other situations that might concern the protection of public health.

Wholesale license shall be suspended or revoked should the Agency that the wholesaler of medicinal products no longer meets the conditions defined in the Law.

Contents of the application and the detailed conditions with respect to space, equipment and staff for obtaining a wholesale license as well as fees to be paid shall be prescribed by the Minister of health

Article 79

Import of medicinal products that have a marketing authorization, clinical trials license or notification does not require import authorization.

As an exemption from the provision of the paragraph 1 of this article, the Agency shall issue an authorization for import of medicinal products in the following situations:

- the medicinal product is on the essential list of products for which a marketing authorization has not been issued
- the medicinal product is immunological medicinal product, radiopharmaceutical product or medicinal product derived from blood even in the cases when marketing authorization was granted
- the medicinal product is required by a hospital or other health institution for treating individual patient or group of patients for which marketing authorization has not been issued
- the medicinal product is needed for continuation of treatment that has been started aboard for which marketing authorization has not been issued
- the medicinal product is needed in exceptional cases e.g. infections, poisoning, radiation etc. or in other cases concerning the interest of protection of public health for which marketing authorization has not been issued
- the medicinal product is used for pre-clinical testing
- the medicinal product is intended for research and development
- medicinal product is designated for further manufacturing and
- the medicinal product is in the smallest packaging and intended for advertisement

Article 80

The applicant for obtaining an authorization for import of medicinal products is importer.

The application for obtaining an authorization for import of medicinal product shall be submitted to the Agency.

The application for obtaining an authorization for import of medicinal product shall contain proof of fulfilling conditions defined in Article 79 and shall be submitted to the Agency.
The Agency shall, within not more than thirty days from the receipt of the application approve or reject it.

The time limit stipulated in paragraph 3 of this article shall be suspended on the day when the Agency requests the clinical trial applicant to provide additional documentation or data that are considered necessary and this suspension of the time limit shall last until the request of the Agency has been met.

Contents of the application, the procedure and the manner of obtaining an authorization for import, as well as fees to be paid shall be prescribed in by the Minister of health

Article 81

Medicinal products are to be retailed in pharmacies.

Retail of medicinal products shall include purchase, storage, keeping and dispensing of medicinal products.

Pharmacies are legal entity. The establishment and the activity of the pharmacies shall be performed according to this Law and to the Health Protection Law.

Retail license is issued by the Minister of Health in accordance with this Law and the Law on Health Protection.

The retail license is issued without time limit

Article 82

Legal entity dealing in the retail of medicinal products shall meet the following requirements:
- to have an appropriate premises, equipment and stuff for retail, corresponding to the quantity and type of medicinal products that are subject to marketing;
- to have employed an adequate number of professionals holding university degree in pharmacy (at least one in every shift that is continuously and permanently present in the pharmacy) and other suitable profiles with appropriate education concerning pharmacy having at least secondary education in pharmacy;
- to keep appropriate records on the consumption of medicinal products;
- to have introduced quality system and organized work processes according to the principles of good pharmacy practice (GPP);
- to meet a product public service obligation e.g. obligation to guarantee permanently and adequate range of medicinal products to meet requirements of the patients on a specific geographical area

If the pharmacies meets the requirements regarding space, equipment and staff stipulated in this law and the Health Protection Law it may prepare, control and dispense magistral and galenic medicinal products.

The pharmacy is obligated to dispense i.e. sell the medicinal products in accordance with the marketing authorization of the medicinal product.

Minister of health shall describe the manner, principles and procedures for retail license.

The Minister of health shall prescribe the procedure, conditions and method for obtaining a retail sale authorization.

The Minister of health shall issue a guideline on the principles of Good pharmaceutical practice

III.5 LABELING AND PATIENT INFORMATION LEAFLET

Article 83

Information on each medicinal product placed on the market must be written in the Macedonian language and its Cyrillic alphabet on its outer packaging or, where there is no outer packaging, on the immediate packaging. Identical information may be given in one or more foreign languages.

The outer packing must contain at the least the basic information on the medicinal product (name and common name, qualitative and quantitative particulars of the active substance, medicinal product form, strength and packing, manufacturer/marketing authorization holder,

manner of use, manner of storage, date of expiry, method of dispensing, medicinal product batch number, marketing authorization number and other relevant identification codes, precaution measures different warnings, price of the medicinal product and other relevant information).

Name of medicinal product, must be written on its outer package also in Braille letter.

The inner packing must contain the basic information on the medicinal product (name and common name, qualitative and quantitative particulars of the active substance, medicinal product form, strength, manufacturer, date of expiry, medicinal product batch number and other relevant information, that are allowed by the size of the inner packing.

Article 84

Every packaged medicinal product placed on the market must contain a patient information leaflet in Macedonian language and its Cyrillic alphabet in line with summary of products characteristics, unless all the information required by the Law is given on the outer package or, where there is no outer package, on the immediate package
The patient information leaflet must contain at least the basic information on the medicinal product (name, common name, qualitative and quantitative particulars, medicinal product form, strength and packing, manufacturer/marketing authorization holder, manner of use, indications, contra-indications, precautions, manner of dispensing, undesirable effects, date of expiry, manner of storage, and other relevant information). Marketing authorization holder must, if required by patient organizations, ensure patient information leaflet appropriate for blind or weak-eyesight patients provided to them properly.

Article 85

As an exception of article 83 of the Law, the Agency may allow outer and inner package and patient information leaflet in foreign language provided that all necessary information is on sticker in Macedonian language and its Cyrillic alphabet and that patient information leaflet in Macedonian language and its Cyrillic alphabet is provided to patients properly.

Article 86

The data placed on the outer and inner package, the structure and the shape and content of patient information leaflet and the cases when stickers may be used shall be prescribed by the Minister of Health

III.6 PHARMACOVIGILANCE

Article 87

The Agency shall establish and maintain the pharmacovigilance system with the database for the purpose of detecting, gathering, monitoring, assessing and responding to new data on safety of medicinal product or investigational medicinal product as well as risk-benefit balance of the use of medicinal product or its interaction with other medicinal products.

The Minister of health shall authorize a legal person for performing the activities of National Center for monitoring of adverse reactions of medicinal products for collection and evaluation of adverse reactions or events, information about interactions or abuse of medicinal products as well as for advising the Agency on measures to be taken.

Article 88

Medical professionals shall be obliged to notify with a legal person from the Article 87 paragraph 2 of this law about any adverse reaction or events or suspicion of adverse reaction or events.

Article 89

Marketing authorization holders shall be obliged to submit periodical safety updated reports to the Agency every six months in the period of two years for any newly received marketing authorization and once a year in the period of following 3 years and than once in three years or upon request of the Agency during validity of marketing authorization.

Article 90

The Minister of health shall prescribe in the method of reporting and the content of the form for reporting adverse reactions, as well as the manner of organization of system of pharmacovigilance.

III.7 ADVERTISING OF MEDICINAL PRODUCTS

Article 91

Advertising of medicinal products shall mean any form of disseminating information about medicinal products to a general or professional public in order to promote prescription of medicinal products, stimulate dispensing of medicinal products, their supply, sale and use.

Article 92

Advertising of medicinal products to medical professionals shall be done by marketing authorization holders through advertisements placed in specialized literature, specialized periodicals and other specialized publications, as well as by direct provision of information to the health care professionals who prescribe or dispense medicinal products.

Advertising of medicinal products subject to medical prescription to medical professionals shall only be allowed in terms of providing information in line the summary of the product characteristics or concerning marketing conditions.

Advertising of medicinal products to medical professionals may be accompanied by provision of one smallest pack of a authorized medicinal product, labeled as being “free of charge and not for sale”, except medicinal products containing narcotic and psychotropic substances.

Article 93

Marketing authorization holders or legal and physical persons acting on their behalf shall not offer gifts, direct or indirect financial or material benefit to persons who prescribe or dispense medicinal products, except if it is of small value and intended for performing healthcare activity.

Marketing authorization holders may enable persons prescribing or dispensing medicinal products to acquire additional knowledge on new medicinal products and already marketed medicinal products, through organizing and holding promotional seminars.

The acquisition of knowledge referred to in the paragraph 2 of this Article must be done in the manner not exceeding the limit of scientific-expert objectives of such an education, must be organizationally subordinated only to acquisition of new findings about medicinal products, and must only be targeted to persons prescribing or dispensing medicinal products.

Article 94

Marketing authorization holders and manufacturers of medicinal products not subject to medical prescription may inform the general public about the medicinal product characteristics in line with summary of product characteristics or patient information leaflet, in an objective manner and upon prior approval by the Agency.

Article 95

It shall be forbidden to advertise to the general public, through the media, those medicinal products that are subject to medical prescription.

As an exemption of the provision of paragraph 1 of this Article and for the purpose of protecting public health or preventing extraordinary situations (epidemic, larger-scale natural disasters etc.), the Director of the Agency, upon proposal by the Medicinal Products Committee, may allow advertising in the media aimed at providing information to a wider public about the use of certain medicinal products.

It shall be forbidden to publicly advertise a medicinal product by associating with its missing characteristics, overstating its positive effects, exaggerating and describing effects of a medicinal product in an inappropriate manner, comparing with other medicinal products or misleading medicinal product users in any other way.

It shall be forbidden to address children while advertising medicinal products.
It shall be forbidden to publicly distribute free samples of medicinal products.
It shall be forbidden to publicly advertise medicinal products that have no marketing authorization.

Article 96

Minister of health shall prescribe the manner of advertising of medicinal products.

Article 97

The Agency shall inform medical professionals about medicinal products that have been granted marketing authorizations in the following manner:

1. by an announcement in the Official gazette of the Republic of Macedonia;
2. by publishing a register of medicinal products in the Republic of Macedonia in the manner allowing its availability to health care professionals and
3. by establishing and maintaining updated database on medicinal products.

The Agency may, if necessary, inform general public on any relevant information concerning the public health.

III.8 QUALITY CONTROL OF MEDICINAL PRODUCTS

Article 98

Quality control of medicinal products shall be aimed to ensure that medicinal products comply with the prescribed standards of quality by evaluating documentation on quality, by laboratory quality control or by inspection.

Quality control of medicinal products shall be conducted in order to determine conformity of medicinal product's quality with the marketing authorization requirements.

Article 99

Quality control of medicinal products shall be performed by medical control laboratories appointed by Minister of health among accredited laboratories.

The control stipulated in paragraph 1 of this article shall be performed in accordance with the European Pharmacopoeia and national supplement thereof or other recognized pharmacopoeias, analytical methods reported by the manufacturer, or other validated analytical methods

Minister of health shall enact the national supplement of European Pharmacopoeia for the Republic of Macedonia.

Article 100

Quality control of medicinal products shall include to the following:

1. Regular quality control of any medicinal product marketed in the Republic of Macedonia, carried out at least once in every five years;
2. Quality control of the first medicinal product batch, carried out after marketing authorization is granted;
3. Quality control of every batch of manufactured, i.e. imported medicinal products batch of medicinal products;
4. Extraordinary quality control, i.e. medicinal product quality control, carried out upon request of the Agency either during the procedure of obtaining a marketing authorization or parallel import license or after their issuance, upon request of the pharmaceutical inspector; and
5. Specific quality control, i.e. control of every batch of specific categories of medicinal products (e.g. immunologicals medicinal products, medicinal products derived from human blood, radiopharmaceutical preparation etc.) upon request by the Agency

Article 101

Medicinal product quality control shall be carried out by the authorized medical control laboratories stipulated in article 99 paragraph 1 of this Law upon proposal by:

1. the Agency;
2. importers, except in the case referred to in Article 75 of this Law provided that the control is carried out by the importers themselves;
3. legal person involved in wholesale distribution of medicinal products;
4. marketing authorization holders.

The laboratories stipulated in article 99 of this Law shall be obligated issue a certificate on the product quality control results, i.e. to inform the entities stipulated in paragraph 1 of this article.
Agency may recognise batch analyses signed by qualified person of some other countries Official Medical Control Laboratories (OMCL) or of a manufacturer in the European Union if an OMCL certificate cannot be provided (for biological medicinal products etc.) and when the manufacturer's laboratory has been accepted by the Agency.

Article 102

Expenses for samples and quality control shall be paid by:

- marketing authorization holder, for regular quality control, quality control of the first medicinal product batch after marketing authorization, specific quality control, i.e. control of every batch of specific categories of medicinal products, quality control of every batch of imported medicinal products;

- the marketing authorization holder for the extraordinary quality control of the medicinal product if it is proved that the quality of the medicinal product is not in accordance with the conditions from the marketing authorization i.e. the declared quality;

- applicant, for marketing authorization for medicinal product during the marketing authorization procedure, if the control required by the Agency

- importer, for quality control of imported batches of medicinal products in line with article 75 of the Law.

Article 103

The manner of quality control of medicinal products, the manner of recognizing of analyses, method of sampling and expenses for quality control as well as the method of keeping evidence, shall be prescribed by the Minister of health

Article 104

Legal entities and natural persons, administrative authorities and organizations, professional institutions that in any way, within their activity, get into possession of medicinal products (transporters, post, customs etc.), shall handle them pursuant to the instructions provided by the customer for the purpose of preventing quality changes or abuse.

Manufacturers, wholesalers/importers, pharmacies or marketing authorization holders shall inform the Agency about quality defect or any other incompliance that could compromise public health.

Marketing authorization holder/importer is obligated to withdraw the concerned product

from the market and perform other activities necessary for protection of health and immediately inform the Agency about all actions taken.

Agency shall monitor all activities of the marketing authorization holder/importer, reacts and report into the international early warning system if necessary for the purpose of protection of health

III.9 DONATIONS OF MEDICINAL PRODUCTS

Article 105

Medicinal products which are subject of donation shall be imported to and used in the Republic of Macedonia, according to the needs only with prior consent of the Minister of health.

The medicinal products referred to in paragraph 1 of this Article shall have a clear and permanent label that the medicinal product is donation and free of charge.

Authorization for import of medicinal products which are donation shall be issued if:

1. there are detailed information concerning every individual medicinal product, including information on the INN and protected name(s) of the medicinal product, its quantity and expiration date,
2. the offered medicinal product type and quantity is needed to the system of health protection, and
3. there is at least one 1 year left until the expiry of the medicinal product.

Medicinal products which are donated, imported to the Republic of Macedonia contrary to the provisions of this Law, shall be returned to the sender, i.e. disposed of at his expense.

The Agency shall ensure an oversight over the equipment, storage and distribution of medicinal products of donation.

III.10. MEDICINAL PRODUCTS WASTE

Article 106

A medicinal product shall be considered defective provided:

1. that it has expired;
2. that its organoleptic characteristics have been changed (appearance, color, taste, smell),
3. that its packing has been damaged,
4. that laboratory control has demonstrated that it does not conform to the declared quality, and
5. that it is withdrawn from use for any other reason.

The defective medicinal product shall be considered pharmaceutical waste and it shall be forbidden to market defective medicinal products.

Pharmaceutical waste shall be disposed of in the manner not jeopardizing health of people and environment.

The expenses associated with disposing of pharmaceutical waste shall be borne by the owner of pharmaceutical waste, i.e. legal or physical person found in possession of the waste.

Detailed requirements concerning the manner of disposing of pharmaceutical waste shall be prescribed by the Minister of health

III.11 PRICING

Article 107

Prices of medicinal products are formed freely, except for the prescription medicinal products and the medicinal products that are on the list of essential medicinal products.

The prescription medicinal products or the medicinal products on the list of essential medicinal products can be marketed if they have been priced in accordance with this Law.

The Minister of Health shall enact a list of essential medicinal products necessary for the health protection.

Article 108

The price forming of medicinal products shall be performed in a manner which is not discriminatory and does not allow dumping.

The price of the medicinal products shall be formed from the following elements:

1. manufacturer's price (hereinafter production price) expressed in denars

2. wholesale margin and

3. retail margin.

The wholesale price of the medicinal products shall be calculated as sum of the elements stipulated in paragraph 2 item 1 and 2, of this article.

The retail price of the medicinal products shall be calculated as sum of the elements stipulated in paragraph 2 of this article.

If the manufacturer supplies the healthcare institutions with medicinal products from its own production program directly, or through his/her own wholesaler in accordance with article 73 paragraph 4 of this Law, the price of the medicinal product shall be identical with the production price of the medicinal product.
If the production price is in the range between 1.00 and 200.00 denars the wholesale margin shall be up to 15% and the retail margin is up to 30% of the production price.

If the production price is in the range between 200.10 and 1000.00 denars the wholesale margin shall be up to 13% and the retail margin is up to 25% of the production price.

If the production price is in the range between 1000.10 and 5000.00 denars the wholesale margin shall be up to 11% and the retail margin is up to 20% of the production price.

If the production price exceeds 5000.10 denars the wholesale margin shall be up to 9%, but not more than 500.00 denars and the retail margin is up to 15% of the production price, but not more than 1000.00 denars.

The entities stipulated in article 18 paragraph 2 of this Law and the importers of medicinal products are obligated to submit the production price of the medicinal product to the Agency.
The Agency shall approve the price within 20 days from the receipt of the application.

The applicant may submit an appeal, within 15 days form the day of receipt of the resolution stipulated in paragraph 6 of this article, to the second instance commission of the Government of Republic of Macedonia in the field of healthcare.

Article 109

Minister of health may in case of an epidemic, natural disasters or emergency situation can determine or control prices of any medicinal products or groups of medicinal products.

Legal persons involved in marketing of medicinal products are obligated to sell medicinal products only at a price formed in accordance with the Law and tax laws.

Article 109

Minister of health may in exceptional cases of public health concern decide to fix or to control prices of any medicinal products or groups of products

Legal persons involved in marketing of medicinal products are obligated to sell medicinal products only at a price formed in accordance with the Law and tax laws.

IV MEDICAL DEVICES

IV.1 CLASSIFICATION OF MEDICAL DEVICES

Article 110

Medical devices shall, in terms of their potential risk for users, be classified into:

1. Class I – medical devices with a low risk potential,
2. Class II-a – medical devices with a high risk potential,
3. Class II-b – medical devices with a higher risk potential, and
4. Class III – medical devices with the highest risk potential.

Article 111

Medical devices shall, according to their nature, power source connection and other characteristics, be classified into:

1. non-invasive,
2. invasive, and
3. active.

Article 112

Medical devices shall, in terms of duration of their use on human beings, be classified into:

1. transitory, used uninterruptedly for less than sixty (60) minutes,
2. short-term, used uninterruptedly for up to thirty (30) days, and
3. long-term, used uninterruptedly for more than thirty (30) days.

Article 113

In vitro diagnostic medical devices shall be classified into:

1. in vitro diagnostic devices used exclusively by health care professionals and classified depending on the device type into list A and list B,
2. in vitro diagnostic devices for self-diagnosis, and
3. all other in vitro diagnostic devices.

Article 114

Medical devices shall, in terms of the manner and place of dispensing, be classified into:

1. medical devices dispensed on prescription order, according to the records in the registry of medical devices, only in pharmacies and specialized stores,
2. medical devices dispensed without prescription order, according to the records in the registry of medical devices, only in pharmacies and specialized stores,

3. medical devices dispensed on prescription order, according to the records in the registry of medical devices, in hospital pharmacies, and
4. medical devices dispensed without prescription on the free market.

Article 115

In case a medical device is presented combined with a medicinal product or can be used as a product for general use, the manner of classification of the products as medicinal product, medical device or a product for general use shall depend on the main purpose and manner of action defined by the manufacturer.

The conditions for and manner of classifying medical devices for the purpose of this Law shall be prescribed in more detail by the Minister of health

IV.2 ESSENTIAL REQUIREMENTS E.G. GENERAL AND SPECIFIC, REQUIREMENTS FOR MEDICAL DEVICES

Article 116

Medical devices must be in accordance with the general requirements concerning safety of products, according to the Law in Products Safety and the requirements prescribed in this Law.

General requirements that a medical device must meet shall include:

1. that it has been designed, manufactured, installed, maintained and used in such a manner that, when used under the prescribed conditions, it meets the original purpose and without compromising health or safety of users,
2. that it has been established a system guaranteeing quality of medicinal product design and manufacturing.

Specific requirements within the meaning of this Law shall mean requirements that medical devices must meet in order to be used for the original purpose.

The general and specific requirements that medical devices should meet shall be prescribed in detail by the Minister of health.

The medical devices shall be considered as safe if they have been produced in accordance with the national standards and published in the list of standards for medical devices.

The Minister of Health shall publish the list of standards for medical devices in the “Official Gazette of the Republic of Macedonia”.

IV.3 MEDICAL DEVICES CONFORMITY ASSESSMENT

Article 117

The procedure for assessing conformity of medical devices, within the meaning of this Law, shall mean a procedure of determining in direct or indirect manner whether medical devices

meet the requirements referred to in the general legislative rules and in this Law.

The procedure of assessing conformity of medical devices with the general and specific requirements shall depend on the medical device classification corresponding to the risk potential and shall be carried out as follows:

1. for medical devices of class I, the manufacturers shall themselves assess the product conformity with the general and specific requirements and draw up on that a conformity declaration, i.e. declaration on EC conformity on their own responsibility. The exceptions shall include medical devices with a measuring mechanism and sterile medical devices, which are treated as medical devices of classes II and III when assessing their measuring function i.e. sterility;

2. for medical devices of classes II-a, II-b and III, the notified body for assessment of conformity shall assess the product conformity with the general and specific requirements and shall issue certificate of EC conformity.

Article 118

Conformity assessment procedure for medical devices shall be performed:

- by conformity assessment authority recognized in the EU e.g. relevant body for conformity assessment

or

- by bodies authorized by the Minister of health on the basis of fulfilling criteria on premises, equipment and staff necessary for conformity assessment procedure of certain type of medical device.

The conditions that need to be fulfilled by the institution performing the conformity assessment for certain types of medical devices shall be prescribed by the Minister of Health.

IV.4 MARKING OF MEDICAL DEVICES

Article 119

Based on the certificate of conformity, medical device manufacturers shall be obliged to mark their products with the prescribed conformity mark.

The provisions stipulated in the Law on Products Safety referring to the conformity mark and the content of the certificate for conformity shall apply to medical devices as well.

Notwithstanding the provision of paragraph (2) of this Article, the manufacturer of a medical device, whose conformity with the general and specific requirements is assessed by a conformity assessment authority recognized i.e. Notified Body in the EU, shall mark the medical device with the EC mark.

Manufacturer of medicinal devices belonging to Class I shall mark his product with EC mark based on the declaration on EC conformity that the product meets the requirements of this Law.

It shall be forbidden to mark a medical device with the mark stipulated in paragraph 3 of this Article, if such marking is not in accordance with this Law.

Article 120

It shall not be necessary to mark medical devices that are intended for clinical trials and custom made medical devices according to article 119 of this Law.

IV.5 MANUFACTURING OF MEDICAL DEVICES

Article 121

Manufacturers of medical devices shall meet the following requirements:

1. that they have notified their activity to the Agency before commencing manufacturing of medical devices and that they have been registered in the Register of manufacturers of medical devices in the Republic of Macedonia
2. that the activity is carried out in a manner ensuring the implemented quality system and the public health protection,
3. to have employed adequate number of professionals with appropriate education concerning the manufacturing of the medical device,
4. that they have a liability insurance for any damage caused to the user or a third person.

5. that they produce only medical devices which are in accordance with the prescribed requirements referred to in the Law.

The requirements concerning premises, equipment, staff for registration of manufacturers as well as fees to be paid shall be prescribed in greater details by Minister of health

Article 122

Manufacturers of medical devices shall be obligated to comply the technical regulations in the process of manufacturing of medical devices to ensure their conformity with the general and specific requirements.

Article 123

The manufacturers of medical devices shall be registered in the Register of medical devices manufacturers if they submit proof for fulfilling of the conditions listed in Art 121 and the following:

- data about the premises, equipment, staff and quality system of the manufacturer,

- address of the manufacturer and confirmation of registration in the Central Registry

- list of medical devices that will be manufactured and their classification which prove that the medical devices are manufactured in a manner ensuring the quality system provision and the public health protection, and in accordance with the general and specific, requirements.

- data about the design, quality control and maintenance method of the medical devices.

- proof of liability insurance for any damage caused to the user or a third person

Agency shall within ninety (90) days inform the manufacturer about the registration into the Register of manufacturers of medical devices.

The deadline stipulated in paragraph 2 of this article shall be suspended on the day when the Agency requests the manufacturer to provide additional documentation or data that are considered necessary and this suspension of the time limit calculation shall last until the request of the Agency has been met.

Manufacturers of medical devices registered in the Republic of Macedonia shall regularly update information submitted and shall report to the Agency all documentation or information concerning all changes in the manufacturing process, specifications of the medical devices, and other information relevant for public health.

Manufacturing shall also involve selling products to legal entities registered for the wholesale activities or natural persons - individual users.

Minister of health shall prescribe the contents of the application and the documentation for entering in the register of manufacturers of medical devices as well fees to be paid.

Article 124

In case a medical device is manufactured abroad, the duty of the manufacturer shall be assumed by the importer of the medical device in the Republic of Macedonia.

IV.4 MARKETING OF MEDICAL DEVICES

Article 125

Marketing of medical devices shall mean import and export, wholesale and retail trade.

Article 126

Wholesale distribution of medical devices shall include purchase, storage, transport, distribution and sale of medical devices, as well as their import and export.

Wholesale distribution of medical devices may only be carried out by legal persons registered the register of wholesale distributors of medical devices.

The legal entities performing wholesale of medical devices shall be allowed to purchase and sell only medical devises that are in conformity with the prescribed essential, general and specific, requirements referred to in the Law and properly marked.

The legal entities performing wholesale of medical devices shall be allowed to purchase and sell medical devices only to legal entities that have been registered the registries of manufacturers of medical devices and legal entities registered in the Register of wholesale and retail sale of medical devices

Article 127

Legal entity dealing in the wholesale of medical devices shall meet the following requirements:

1. they have notified their activity to the Agency before commencing wholesaling of medical devices and they have been entered in the Register of wholesalers of medical devices in the Republic of Macedonia
2. to have employed an adequate number of professionals with university level education in the field of medicine, pharmacy and dentistry,
3. the wholesale activity is carried out in a manner ensuring the implemented quality system and the public health protection,
4. they have an employed a person who is responsible of monitoring and reporting undesirable effects and reactions according to the provisions of the Law and they have employed adequate number of persons with appropriate education regarding the sale of medical devices,
5. that wholesaled medical devices are in conformity with the prescribed general and specific requirements referred to in the Law and the medical devices are properly marked.

Article 128

Notification for wholesalers of medical devices in the Republic of Macedonia shall contain documents proving that conditions listed in the article 127 of this Law are met and the following data:
- address of the wholesaler and confirmation of registration in the Central Registry and

- list of medical devices that will be wholesaled and their classification.

Article 129

Agency shall within ninety (90) days inform the wholesaler about entering into the Register of wholesalers of medical devices.

The deadline stipulated in paragraph 1 of this article shall be suspended on the day when the Agency requests the wholesaler to provide additional documentation or data that are considered necessary and this suspension of the time limit calculation shall last until the request of the Agency has been met.

Wholesalers of medical devices registered in the Republic of Macedonia shall regularly update information submitted and shall report to the Agency all documentation or information concerning all changes in the wholesale activities relevant for public health.

The detailed conditions concerning premises, equipment, staff and notification documentation for registration of wholesalers shall be prescribed in greater details by Minister of health as well as fees to be paid.

Article 130

Retail trade of medical devices shall include purchase, storage, keeping and sale of medical devices to individual users.

Medical devices may be retailed in pharmacies and/or specialized shops.

Retail sale of medicinal products in pharmacies shall be appropriately applied to retail sale of medical devices in pharmacies.

Legal entities involved in retail trade with medical devices may purchase medical devices only from the medical devices wholesalers recorded in the register of wholesalers of medical devices.

Specialized stores dealing in the retail trade of medical devices shall meet the following requirements:

1. that they have notified their activity to the Agency before commencing retail trade with medical devices and that they have been entered in the Register of specialized stores for medical devices,
2. that the activity is carried out in a manner ensuring the public health protection,
3. to have employed an adequate number of professionals of suitable profiles and with appropriate education,
4. that they have an employee with, at least, the secondary education degree in the field of medicine, pharmacy or dentistry should she/he be responsible for medical devices and in charge of monitoring and reporting undesirable effects and reactions to them, and
5. that sale of medical devices is in conformity with the prescribed general and specific requirements referred to in the Law and properly marked.

Following the notification containing proofs of fulfilling conditions listed in the paragraph 5 of this article, the Agency shall within ninety (90) days inform the legal entity about entering into the Register of specialized shops of medical devices in the Republic of Macedonia.

The deadline stipulated in paragraph 6 shall be suspended on the day when the Agency requests the applicant to provide additional documentation or data that are considered necessary and this suspension of the time limit calculation shall last until the request of the Agency has been met.

Specialized stores of medical devices registered in the register of specialized shops shall regularly update information submitted and shall report to the Agency all documentation i.e. information concerning all changes in the retail trade activities relevant for public health.

In accordance with this Law, requirements concerning premises, equipment, staff and notification documentation for registration of specialized stores for medical devices as well as fees to be paid shall be prescribed in greater details by Minister of health

Article 131

The Agency shall keep a register of manufacturers, legal persons involved in wholesale distribution and retail trade of medical devices, as well as a register of medical devices available on the market in the R of Macedonia.

The contents of the register from the paragraph 1 of this article, the availability of the data from the register as well as expenses associated with recording shall be prescribed by the Minister of health.

IV.5 LABELLING OF MEDICAL DEVICES

Article 132

All medical devices marketed must be labeled according with the provisions of this Law on the outer and inner packing in Macedonian language and its Cyrillic alphabet and must contain instructions for use.

A packing of medical devices must contain at least the following:

- information on the manufacturer, i.e. importer;

- information necessary for the identification of the medical device and contents of the packing;

- necessary labels like “sterile”, “custom-made”, “single use”, “for clinical trials”, etc.;

- identification code;

- expiry period;

- storage conditions;

- special method of use;

- warnings; and

- purpose and other information related to the proper use of the device and public health protection.

The instructions for use of medical devices must be written in Macedonian language and its Cyrillic alphabet.

In addition to the information referred to in paragraph (2) of this Article, must at least contain the information on undesirable effects, details concerning the proper installation and check up of proper use, as well as other information pertaining to medical devices.

Contents and the manner of labeling the outer and inner packing of medical devices, as well as contents of the instructions for use, shall be prescribed in grater details by Minister of health.

IV.6 CLINICAL TRIALS OF MEDICAL DEVICES

Article 133

Clinical trials of medical devices shall refer to establishing or confirming safety of medical devices, their usefulness and conformity with the essential, general and specific, requirements pursuant to the purpose defined by the manufacturer.

Clinical trials of medical devices may only be carried out by legal entities that meet the requirements pertaining to premises, equipment and staff, as well as other requirements and principles of good practices and are authorized by Minister of health for those activities.

The procedure of clinical trials of medical devices must conform to modern scientific and technical developments, shall be performed in accordance with ethical principles of the Declaration of Helsinki and other ratified international agreements, in accordance with principles of good clinical practice and in accordance with mandatory and guaranteed protection of personal data and rights of investigational subjects.

The documents on clinical trials of medical devices should contain the trials results that are described sufficiently and objectively to allow an objective evaluation of the risk-benefit balance for a patient, evaluation of medical device safety and usefulness, as well as an opinion on whether medical devices conform to the general and specific, requirements of this Law and the purpose defined by its manufacturer.

Individuals subject to clinical trials must be informed on all relevant details on the trials, about the purpose of the trial, its nature, the procedure and the potential risk involved, in a way understandable to them and in writing.

The clinical trial of the medical device may be performed only if the subject gives written consent.

The consent stipulated in paragraph 6 of this article may be revoked at any time.

Before commencing clinical trials, legal entities carrying out and sponsoring clinical trials must insure the subjects from the liability for any damage possibly caused to the investigational subjects in the course of clinical trials in accordance with the general regulations for liability insurance.

Article 134

Before commencing a clinical trial of a medical device, the intended clinical trial of the medical device must be notified with the Agency by the sponsor or its authorized representative.

The notification of clinical trial shall contain summary of information on the medical device, all necessary information on results of tests of safety of the product and results of clinical trials on the device concerned or similar device, clinical trials protocol, agreement of the National ethics committee, informed consent, information to user and other information necessary for decision on notification or rejection of the trial

Should the Agency fail to respond negatively to the application for a clinical trial of a medical device within thirty (30) days from the date of its receipt, it shall be considered that the applicant is allowed to commence the clinical trial of the medical device.

The Agency shall inform the applicant of the reasons for refusing the proposed clinical trial of a medical device within not more than thirty (30) days from the receipt of a complete application,

The time limit referred to in paragraph (4) of this Article shall be suspended on the day when the Agency requests the clinical trial applicant to provide additional documentation or data that are considered necessary, and this suspension of the time limit calculation shall last until the request of the Agency has been met.

Article 135

Sponsor or his authorized representative must notify with the Agency all relevant changes of the clinical trials

If the sponsor or his authorized representative does not receive a negative response from the Agency within thirty (30) days, it may introduce the change.

Article 136

In the case of unexpected serious adverse reaction or event occurred during a clinical trial, the sponsor shall immediately inform the Agency, the National ethics committee and legal person from the second paragraph of article 87 paragraph 2 of this Law.

For the purpose of public health protection, the Agency may order a temporary or permanent suspension of clinical trials, oversight over clinical trials, and conformity of clinical trials with the principles of good practice and trial protocol, in accordance with this Law.

Article 137

Required documentation and manner of notification of clinical trials, changes of notified clinical trials, reporting adverse reactions and events or incidents, requirements that shall be met by legal entities entitled to carry out clinical trials of medical devices as well as fees associated with the procedures shall be prescribed by the Minister of health

IV.7 MATERIOVIGILANCE

Article 138

The provisions of Article 87 through 89 of this Law, which apply to pharmacovigilance, shall also be appropriately applied to medical devices, i.e. the system of materiovigilance.
Minister of health shall describe in greater details the manner of reporting undesirable effects during the use of medical devices, types of reactions to them, duties of medical staff and suppliers, as well as manner of organizing a system of monitoring undesirable effects of medical devices and reactions to them.

IV.8 ADVERTISING OF MEDICAL DEVICES

Article 139

The provisions of Chapter III.7 of this Law, which concern advertising of medicinal products,

shall also be appropriately applied to medical devices.

It is prohibited to advertise in public medical devices which are used only by healthcare institutions.

The Minister of health shall prescribe in great details the manner of advertising medical devices to general and professional public

IV.9 DONATIONS OF MEDICAL DEVICES

Article 140

The provisions of Chapter III I of this Law, which concern donations of medicinal products, shall also be appropriately applied to medical devices.

V INSPECTION

Article 141

The supervision of the implementation of this Law shall be performed by the Ministry of Health.

Inspection of the implementation of this Law shall be carried out by the Agency through pharmaceutical inspectors.

Notwithstanding provision of the paragraph 2 of this article, inspection concerning pricing of medicinal products shall be carried out by financial inspectors together with pharmaceutical inspectors.

Notwithstanding provision of the paragraph 2 of this article, inspection of import of medicinal products is carried out by customs officers together with pharmaceutical inspectors.

Article 142

Pharmaceutical inspector may be a person fulfilling the conditions determined in the Civil Servants Law and shall have a university degree in pharmacy and minimum of three (3) years of relevant experience in the profession.

The Minister of Health shall appoint the Pharmaceutical inspectors in accordance with the Civil Servants Law.

The Agency, may engage experts in the field of pharmacy, medicine or other relevant fields to carry out individual expert activities of importance for the pharmaceutical-inspection prior, during or after the inspection.

The pharmaceutical inspector shall be independent, within his/her rights and obligations.

Article 143

The inspection supervision shall be performed regularly, systemically in accordance with a predetermined plan, as well as in case of suspicion.

The inspection supervision shall be performed without a prior announcement.

Article 144

The pharmaceutical inspector shall prove his/her official status with an identification card.

The form and the content, as well as the way of issuance and revocation of the identification card shall be prescribed by the Minister of Health.

Article 145

The pharmaceutical inspector shall pass a decision determining the measures for which he/she is authorized, in accordance with the regulations for the general administrative procedure, unless otherwise regulated by this law.

The legal entities shall be obligated to implement the measures contained within the decision of the inspector.

The appeal against the decision does not suspend the enforcement of the decision.

The appeal against the decision of the pharmaceutical inspector in the second instance shall be resolved by the Minister of Health.

In case of a violation of the provision stipulated in paragraph 1 of this article, the pharmaceutical inspector shall be responsible for a violation of official authorization in accordance with the law.

V.1 INSPECTION OF MEDICINAL PRODUCTS

Article 146

Pharmaceutical inspector, during the inspection of medicinal products, shall have the following competence:

1. to issue a ban or a temporary ban on manufacturing, testing or marketing of medicinal products or a specific batch of a medicinal product on the grounds of non-conformity with prescribed conditions,
2. order a legal entity to bring their operations in line with the requirements set out in the Law within the maximum of 6 month from the receipt of the order calling for this measure,
3. to prohibit marketing of medicinal products or a specific batch of medicinal product that does not comply to prescribed conditions, is harmful under prescribed conditions for use, has no therapeutic effect or has unfavorable risk/benefit ratio under prescribed conditions for use,
4. to order the destruction of a defective medicinal product in line with regulations on environmental protection,
5. to ban the import of a medicinal products which has not been granted marketing authorization, parallel import authorization or import authorization granted

by the Agency or which has been transported contrary to the manufacturer's instructions,
6. to take a sample of a medicinal product for the control purposes referred to in this Law,
7. to order a temporary withdrawal of a medicinal product, i.e. its specific batch from the market or to confiscate it until the final ruling of the Agency, if suspected that it does not meet the prescribed quality,
8. to confiscate medicinal products that are manufactured or marketed by legal entities not in possession of manufacturing or wholesale authorization,
9. to prohibit any advertising of medicinal products which is inconsistent with this Law and to order the removal or destruction of the material used for advertising of medicinal product,
10. to identify the violator of the provisions of this Law and acquire his personal data,
11. to order ban of clinical trial of medicinal product in the trial is not in line with this Law,
12. to order other measures and determine deadlines for their implementation due to harmonization of the legal entities with this law and regulations enacted based on this law and
13. in case of breech of the provisions of this law, initiate a misdemeanor procedure in front of relevant court.

The inspector, who during the inspection finds elements of crime, is obligated to inform the competent authority immediately.

Article 147

The legal entities whose work is subject of supervision according to this Law are obligated to enable uninterrupted performance of the supervision, to make available the necessary samples of their medicinal products, free of charge, as well as the necessary data regarding the supervision.

When undertaking an inspection oversight, the pharmaceutical inspector shall have the right and duty to directly examine business and other premises, equipment, work process, products and other goods, identification documents and other documents, to confiscate products, documents or samples for the purpose of protecting evidences and data, as well as to undertake other activities within the framework of his/her authorizations.

During the inspection, the pharmaceutical inspector shall have the right to enter the premises of manufacturers, their representatives, wholesalers, retail sellers, and marketing authorization holders regardless of official hours and their presence, without permission of the legal person concerned for the purpose of inspection.

Pharmaceutical inspector shall have the right to ask support from police if necessary.

Article 148

The license for work of the legal entity shall be revoked if some of the administrative measures stipulated in article 146 of this law, with a legally effective decision of the pharmaceutical inspector, are imposed against it for the second time, with a legally effective decision of the pharmaceutical inspector.

The decision for the revocation of the license for work shall be passed by the Agency.

An appeal may be lodged against the decision stipulated in paragraph 2 of this article to the Minister of Health.

The legal entity whose license for work is revoked shall be deleted from the relevant Register.

Article 149

The pharmaceutical inspector may decide that the drugs which were banned from marketing shall remain for safekeeping in the entity where they were found.

The drugs stipulated in paragraph 1 of this article shall be kept separately, properly packaged and marked.

The pharmaceutical inspector shall enclose in the minutes of the sampling, an inventory of the drugs stipulated in paragraph 1 of this article.

As an exception from paragraph 1 of this article, and for safety purposes, the pharmaceutical inspector may confiscate the drugs which he/she banned from marketing.

Article 150

The pharmaceutical inspector shall take minutes of every inspection oversight, specifying the state of facts established during the inspection oversight

The pharmaceutical inspector may take decision-minutes, in the following cases:

1. when the risk to the public health or lives demands an immediate measure,
2. when there is a risk of hiding, replacing or destroying evidence if the measure is not taken immediately.

The pharmaceutical inspector shall enact a resolution within 48 hours after the order in cases stipulated in paragraph 2 of this article.

The decision stipulated in paragraph 3 of this article may be appealed against to the Minister of Health within eight (8) days from the day of receipt of the decision.

The appeal shall not delay the enforcement of the decision.

Article 151

In the case of decision of legal persons that manufacture or market medicinal products or are granted marketing authorization for medicinal product not to place the medicinal product or to cease to supply the medicinal product due to its pricing, the pharmaceutical inspector can order marketing or further marketing of the products, if it would seriously jeopardize the supply of medicinal products and have negative consequences on public health, for a period of maximum three (3) months.

The legal entity responsible for price of the marketed medicinal product, that markets the

products against provisions on pricing set up in this Law shall 15 days after the inspectors stipulated in article 141 paragraph 3 order bring the price of the medicinal product in line with the provision and to pay the difference between the two prices.

Article 152

The pharmaceutical inspector shall be obligated to keep as classified information all facts and data which he/she uncovered during the inspection supervision, and which are confidential or represent a secret with respect to the interests of the legal entity.

V. 2 INSPECTION SUPERVISION FOR MEDICAL DEVICES

Article 153

Provisions of Chapter V.1 of this Law shall also be appropriately applied to medical devices.

The pharmaceuticals inspectors shall have the right and duty to undertake the following measures:

1. to monitor the system of quality control used by the manufacturer of a medical device and, if needed, the premises of the supplier or other contracting party of the manufacturer,
2. to order appropriate tests of a medical device to assess its conformity with this Law and the Law on product safety upon its marketing or commencement of its use,
3. to take a sample of a medical device and to order an assessment of its conformity in an authorized body for assessment of the conformity in order to verify the conformity with the prescribed conditions,
4. to ban or temporary ban on manufacturing, testing or marketing of a medical device due to its failure to meet the prescribed requirements, i.e. for jeopardizing public health,
5. to temporary ban on marketing of a medical device that is inconsistent with the prescribed requirements or in other cases envisages by this Law,
6. to temporarily ban the work of a legal person for the lack of conformity with the prescribed requirements,
7. to confiscate medical devices that are manufactured or marketed by legal entities not entered in the register of manufacturers,
8. to prohibit any advertising of a medical device that is contrary to this Law and to order removal or destruction of the entire advertising material for the medical device,
9. to prohibit the activity of a legal entity whose organization and activities have not been harmonized with this Law within the given time period,
10. to order destruction of medical devices that are not for use in the manner and under the conditions laid down in this Law in accordance with the regulations on waste management ,
11. to order correction of irregularities and deficiencies,
12. to prohibit activities inconsistent with this Law,
13. to order ban or temporary ban of clinical trial of medical device if the trial is not in line with this Law
14. to order other measures in accordance with this Law.

VI MISDEMEANOR SANCTIONS

Article 154

A legal entity shall be fined by paying EUR 25,000 to 50,000 in MKD equivalent for misdemeanor if:

1. markets medicinal products contrary to article 11 paragraph 1 and 3 and article 17 paragraph 1 of this Law;
2. markets products which are represented with characteristics described in the definition of the medicinal products for prevention or treatment of diseases or situations, but they are not classified as medicinal products within the meaning of this Law (article 12);
3. markets medicinal product which has not been produced and controlled in accordance with the requirements of article 16 of this Law;
4. fails to establish and maintain pharmacovigilance system and fails to appoint a person responsible for pharmacovigilance who will be permanently and continuously accessible (article 19 paragraph 3);
5. appoints person responsible for pharamacovigilance who does not possess university degree in the field of medicine or pharmacy (article 19 paragraph 4);
6. performs clinical trials of medicinal products contrary to the ethical principles of the Helsinki Declaration and to other signed international agreements and/or principles of the good clinical practice and/or contrary to the mandatory and guaranteed protection of the personal data and rights of the trial subjects (article 54 paragraph 2);
7. performs clinical trials of medicinal product without submitted results from the analytical and pharmacological and toxicological investigation or trials of medicinal product which influences the human genetic code (article 54 paragraph 1)
8. fails to insure the trial subjects before the commencement of the trial for the risks of damage of the health of those persons, caused by the clinical trial of the medicinal product (article 57 paragraph 3)
9. fails to report to the Agency, all the relevant changes in the clinical trail (article 60 paragraph 1);
10. in case of unexpected serious adverse reactions or events which occurred during the clinical trail fails to inform the Agency, Ethical committee and legal entity of article 87 paragraph 2 of this Law (article 61);
11. produces medicinal products without having manufacturing authorization (article 65 paragraph 1, 2 and 3);
12. produces medicinal products without fulfilling the conditions of article 68 of this Law;
13. fails to enable regular inspection supervision, as well as supervision on Agency's request (article 71 paragraph 1);
14. fails to inform the Agency about all incidents or mistakes occurred in the manufacturing process or other situations which are of interest for the public health (article 71 paragraph 2);
15. fails to procure medicinal products only from legal entities who have manufacturing authorization or wholesale authorization or sells to legal entities who do not possess authorization for wholesale or retailing of medicinal products (article 73 paragraph 3);
16. supplies, sales or distributes medicinal products with marketing authorization or medicinal products with import license or medicinal products for approved

clinical trials as well as medicinal product for further processing, cumulating the determined wholesale fee (article 73 paragraph 5) or performs retail trade (article 73 paragraph 6)

17. performs wholesale distribution of medicinal products without possessing wholesale authorization for medicinal products (article 73 paragraph 2)
18. performs wholesale of medicinal products without fulfilling the conditions stipulated in article 74 of this Law, i.e. performs import of medicinal products without fulfilling the conditions stipulated in article 74 of this Law and does not have own accredited laboratory or contract with authorized laboratory for investigation and control of medicinal products (article 75 paragraph 1 and 2) or does not possess manufacturing authorization for the processes it performs (article 75 paragraph 3);
19. fails to inform the Agency for any change regarding the conditions stipulated in article 74 of this Law (article 77 paragraph 1);
20. imports medicinal product without import authorization in cases stipulated in article 79 paragraph 2 of this Law;
21. performs retailing of medicinal products without fulfilling of the conditions stipulated in article 82 of this Law;
22. markets medicinal product which has not been marked in accordance with article 83 of this Law and/or does not contain patient information leaflet according to article 84 of this Law;
23. fails to inform the legal entity stipulated in article 87 paragraph 2 of this Law and the Agency on any serious adverse reaction or event or suspicion of any serious adverse reaction or event occurred in the Republic of Macedonia or in other countries (article 89 paragraph 1);
24. offers direct or indirect financial or material benefit to the persons who prescribe or administer the medicinal products (article 93 paragraph 1);
25. advertises prescription only medicinal products to the general public through the mass media (article 95 paragraph 1);
26. advertises medicinal product in a manner contrary to article 95 paragraph 3 of this Law misleading the user of the medicinal product;
27. publicly advertises medicinal products through addressing children (article 95 paragraph 4);
28. publicly distributes free samples of medicinal products (article 95 paragraph 5)
29. publicly advertises medicinal products without marketing authorization (article 95 paragraph 6);
30. fails to provide conditions for storage and keeping in accordance to the conditions prescribed by the manufacturer in order to prevent changes in the quality or abuse (article 104 paragraph 1);
31. fails to inform the Agency as well as the other relevant entities for change in the medicinal product's quality and/or other inappropriateness which could endanger the public health (article 104 paragraph 2)
32. fails to withdraw from the market the medicinal product stipulated in article 104 paragraph 2 of this Law, fails to undertake all the necessary activities for protection of the health and fails to inform the Agency on all activities undertaken (article 104 paragraph 3);
33. imports and uses medicinal products from donations of humanitarian origin without previous consent from the Minister of health (article 105 paragraph 1) and/or does not have permanent and clear mark that the medicinal products if of humanitarian origin and free of charge (article 105 paragraph 2);

34. markets defective medicinal products (article 106 paragraph 2)
35. acts contrary to article 108 paragraph 5 of this Law,
36. fails to submit the production prices of the medicinal product to the Agency (article 108 paragraph 10)
37. sales medicinal products at price which has not been formed according to this Law (article 109 paragraph 2);
38. markets medical device which is not in accordance with the conditions stipulated in article 116 of this Law;
39. fails to mark its marketed products with the prescribed conformity mark, based on the conformity certificate (article 119 paragraph 1);
40. marks medical device with the CE mark and such marking is not in accordance with this Law (article 119 paragraph 5);
41. manufactures medical devices without fulfilling the conditions stipulated in article 121 of this Law and/or fails to submit the documentation stipulated in article 123 paragraph 1 of this Law;
42. fails to obey the technical regulations in the manufacturing process of medical devices in order to provide conformity of the medical devices with the general and special conditions (article 122);
43. wholesales medical devices without being registered in the Register of legal entities for wholesale of medical devices (article 126 paragraph 2);
44. buys and sells medical devices contrary to the article 126 paragraph 3 and 4 of this Law;
45. wholesales medical devices without fulfilling the conditions stipulated in article 127 of this Law;
46. markets medical device which is marked and/or contains instructions for use contrary to article 132 of this Law;
47. performs clinical trails of medical devices without fulfilling the conditions and principles of good practices stipulated in article 133 paragraph 2 of this Law;
48. implements procedure for clinical trails of medical devices contrary to article 133 paragraph 3 of this Law;
49. commences with clinical trials of medical device without reporting it to the Agency (article 134 paragraph 1);
50. fails to inform the Agency about all relevant changes of clinical trials (article 135 paragraph 1);
51. fails to inform the Agency, the Ethical Committee and the legal entity stipulated in article 87 of this Law in case of adverse, serious, unexpected reactions i.e. cases which have occurred during the clinical trial (article 136 paragraph 1);
52. advertises medical devices which are used only in healthcare institutions (article 139 paragraph 2).

The responsible person in the legal entity shall also be fined for the misdemeanor stipulated in paragraph 1 of this article in amount of EUR 10,000 to 20,000 in MKD equivalent.

The employee in the legal entity who has committed the misdemeanor stipulated in paragraph 1 of this article shall be fined in amount of EUR 6,000 to 10,000 in MKD equivalent.

Article 155

A legal entity shall be fined by paying EUR 15,000 to 30,000 in MKD equivalent for misdemeanor if:

1. fails to inform the Agency about the date of commencement of the marketing of the medicinal products (article 30 paragraph 2)
2. fails to inform the Agency not later than two months before the cease of production or marketing of the medicinal product before it decides to manufacture or market the medicinal product before the expiration of the marketing authorization (article 36)
3. fails to regularly inform the Agency about every smaller changes of type IA and type IB in the procedure for marketing (article 39);
4. performs analytical, pharmaco-toxicological and clinical trials contrary to article 50 of this Law;
5. performs paharmaco-toxicological i.e. preclinical trials of the medicinal product contrary to the principles of good laboratory practice (article 52 paragraph 1);
6. fails to inform the individuals subject of the clinical trials about all relevant data on the trial, the goals of the trial, its nature, the procedure and the possible risk in a manner which is understandable to them and in written form (article 55 paragraph 1);
7. fails to inform the Agency prior to commencement of the clinical trial and/or about performing bioequivalent studies (article 59 paragraph 1);
8. fails to inform the Agency about any change regarding the conditions stipulated in article 68 of this Law (article 70);
9. fails to provide data about the quantity of medicinal products sold, as well as other necessary data regarding the sale of the medicinal product (article 72 paragraph 2);
10. fails to inform the Agency about all incidents or mistakes in the work process or about other situations which are of interest for the public health (article 78 paragraph 2);
11. fails to submit periodical reports on the safety of the medicinal product, every six months, in the first 2 year period, once a year in the following three years and once any three years until the expiration of the authorization or upon Agency's request (article 89 paragraph 2);
12. advertises medicinal products or medical devices contrary to article 92 of this Law;
13. provides information about the goals stipulated in article 93 paragraph 2 in a manner contrary to article 93 paragraph 3 of this Law;
14. fails to advertise the medicinal products according to article 94 of this Law;
15. fails to issue confirmation of the quality control of the medicinal products i.e. fails to inform the entities stipulated in article 101 paragraph 1 of this Law (article 101 paragraph 2);
16. fails to perform regular update of the submitted information and fails to submit to the Agency all the documents i.e. information regarding all changes in the production process, the specifics of the medical devices as well as all other information relevant for the public health (article 123 paragraph 4);
17. fails to perform regular update of the submitted information and fails to submit to the Agency all the documents i.e. information regarding all changes in the activities of the wholesale of medical devices, relevant for the public health (article

129 paragraph 3);
18. buys medical devices from legal entities which are not registered in the Register of legal entities for wholesale of medical devices (article 130 paragraph 4);
19. performs retailing of medical devices without fulfilling the conditions (article 130 paragraph 5);
20. fails to perform regular update of the submitted information and fails to submit to the Agency all the documents i.e. information regarding all changes in the activities of the retailing of medical devices, relevant for the public health (article 130 paragraph 8)

The responsible person in the legal entity shall also be fined for the misdemeanor stipulated in paragraph 1 of this article in amount of EUR 8,000 to 15,000 in MKD equivalent.

The employee in the legal entity who has committed the misdemeanor stipulated in paragraph 1 of this article shall be fined in amount of EUR 6,000 to 10,000 in MKD equivalent.

Article 156

Healthcare professional shall be fined in amount of EUR 6,000 to 10,000 in MKD equivalent if he/she fails to inform the legal entity, stipulated in article 87 paragraph 2 of this Law, about all adverse reactions or events or in case of suspected adverse reaction or event in accordance with this Law (article 88).

VII TRANSITIONAL AND FINAL PROVISIONS

Article 157

The Agency for medicinal products shall begin to operate starting from 1st of January 2010.

Until the start of operations of the Agency the Bureau for Pharmaceuticals shall continue to perform the activities under the responsibilities of the Agency for Medicinal Products.

Until the start of operations of the Agency for medicinal products, the appeals lodged against the first instance decisions enacted in accordance with this Law shall be resolved by the Minister of health.

Article 158

The manufacturers and legal entities that perform wholesale and retail trade of medicinal products and medical devices are obligated to harmonize their activity with the provisions of this Law within six months from the day when this Law becomes effective.

Article 159

The requirements for manufacturing and sale of medicinal products and medical devices as well as the requirements for marketing of medicinal products and medical devices submitted before the day when this Law becomes effective shall be processed according to the provisions of the regulations which have been effective in the time of submission of the request.

Article 160

The provisions of articles 14 paragraph 2, 25, 75 and 79 or this Law shall apply after 2 years from the day when this Law becomes effective.

Article 161

The article 20 of this Law regarding the harmonization of the documentation for medicinal products which already have a marketing authorization shall apply from 1st of January 2010.

Article 162

The article 22 paragraph 1 item 2 of this Law with respect to exclusivity of the data, exclusivity in the market and the additional new indication shall start to apply after the expiration of eight years from the day this Law becomes effective.

Until the start of application of article 22 paragraph 1 item 2 of this Law upon a request for marketing authorization of a medicinal product:

- in a period of two years from the day this Law becomes legally effective the data exclusivity, exclusivity in the market and additional new indication shall not apply
- in a period of two to four years from the day this Law becomes legally effective data exclusivity of two years and market exclusivity of three years shall apply,
- in a period of four to six years from the day this Law becomes legally effective data exclusivity of four years and market exclusivity of five years shall apply,
- in a period of six to eight years from the day this Law becomes legally effective data exclusivity of six years and market exclusivity of seven years shall apply,

Article 163

The provision of article 37 paragraph 5 of this Law shall apply starting 5 years after this Law becomes effective.

Article 164

The provision of article 83 paragraph 3 of this Law shall apply starting 5 years after this Law becomes effective.

Article 165

Until the accreditation of the laboratories according to the accreditation regulations, the testing and analysis of the medicinal products shall be performed by the existing authorized laboratories.

Article 166

The marketing authorizations issued based on the regulations applicable in the time when the authorization has been issued, shall stay valid until the expiration of the validity of the marketing authorization.

The holders of marketing authorization of medicinal products shall be obligated within 30 days from the day of legal effectiveness of this law to submit an application for forming the

price of the medicinal products in accordance with the provisions of this Law.

The Agency shall approve the price of the medicinal products within 120 days from the day when the application was submitted.

If the holder of the marketing authorization of the medicinal product fails to file an application within the deadline stipulated in paragraph 2 of this article, the marketing authorization shall be revoked.

Article 167

The marketing authorizations for medical devices issued based on the regulations applicable in the time when the authorization has been issued, shall be harmonized with this Law within three years from the day when this Law becomes effective.

Article 168

The Minister of Health shall enact the bylaws envisaged in this Law not later than sic months from the day when this Law becomes effective.

The existing regulations shall apply until the enactment of the bylaws stipulated in paragraph 1 of this article.

Article 169

On the day of legal effectiveness of this law, the provisions from the Law on drugs, auxiliary medical products and medical devices (“Official Gazette of the Republic of Macedonia number 21/98”), related to medicinal products for human use shall cease to apply.

Article 170

This Law shall become effective on the eighth day after its publication in the Official Gazette of the Republic of Macedonia.