LEGEND: XXXXXX= PURE NATIONAL PROVISIONS (NOT DEPENDING OF EU LEGISLATION)
XXXXXX= FORESEEN BY-LAWS
XXXXXX = MODIFICATIONS

Republic of Macedonia
Ministry of Health

DRAFT 02

LAW ON MEDICINAL PRODUCTS AND MEDICAL DEVICES

FEBRUARY 2007

I GENERAL PROVISIONS

Article 1

This Law shall regulate medicinal products and medical devices for use in human medicine, conditions and measures for ensuring their quality, safety and efficacy, conditions and procedures for their manufacturing, testing, marketing, pricing, control, advertising, inspection and other matters of relevance for this domain.

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 animals, parts of organs, animal secretion, toxins, extracts, blood products
- Vegetable, e.g. micro-organisms, plants, parts of plants, vegetable secretion, extracts,
- Chemical, e.g. elements, naturally occurring chemical materials and chemical products obtained by chemical change or synthesis

3. NAME OF THE MEDICINAL PRODUCT is the name that may be either an invented name not liable to confusion with the common name, or a common

or scientific name accompanied by a trade mark or by the name of marketing authorization holder.

4. 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.

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

6. 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 supplied directly to the patients served in the pharmacy in question.

7. HOMEOPATHIC MEDICINAL PRODUCT is any medicinal product prepared from substances or called homeopathic stocks in accordance with a homeopathic manufacturing procedure described by the European Pharmacopoeia, National supplement of the Ph.Eur. (Herein after the National Suplement) or in the absence thereof, by pharmacopoeias currently used officially in counties that have the same standards of quality of homeopatic medicinal products. A homeopatic medicinal product may contain a number of principles.

8. 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.

9. 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).

10. HERBAL PREPARATIONS are preparations obtained by subjecting herbal substances to treatments such as extraction, destilation, squeezing, expression, fractionation, purification, contentration or fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential opis, expressed juices and processed exudates

11. TRADITIONAL HERBAL MEDICINAL PRODUCTS are medicinal products which fulfil 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 for diagnostic purposes or for prescription or monitoring of treatment
- they are exclusively for administration in accordance with a specified strength and posology
- 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 15 years in R of Macedonia or in the EU or countries with the same level of requirements for quality ans safety of those products.
- 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.

12. PHARMACOPOEIA is a list of provisions 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.

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

14. EXCIPIENS: …is a substance other than active substance which is included in the manufacturing process or contained in a finished pharmaceutical form of a medicinal product

15. GENERIC MEDICINAL PRODUCT is a medicinal product which has the same qualitative and quantitative composition in active substances 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, unless such study is judged as unnecessary by scientifically accepted guidelines. 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.

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

17. MEDICINAL PRODUCT DERIVED FROM HUMAN BLOOD OR HUMAN PLASMA is any medicinal product based on blood constituents in particular albumin, coagulating factors and immunoglobulins.

18. BLOOD AND BLOOD PREPARATIONS 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 products that under this Law do not require marketing authorization.

19. RADIOPHARMACEUTICAL is any medicinal product which, when ready for use, contains one or more radionuclides (radioactive isotopes) incuded for a medicina purpose.

20. 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.

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

22. RADIONUCLIDE PRECURSOR is any other radionuclide produced for radio-labeling of another substance prior to administration.
23. IMMUNOLOGICAL MEDICINAL PRODUCT is a medicinal product consisting of vaccines, toxins and serums or allergen products.

24. 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.

25. 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.

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

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

28. 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.

29. GOOD TRANSPORT PRACTICE (GTP) is a qualitative system governing the organization, implementation and control of transport of medicinal products from the manufacturer to the end user.

30. GOOD STORING PRACTICE (GSP) is a qualitative system governing the organization, implementation and control of storage of medicinal products and medicinal devices under a defined regime.

31. 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 of data acquired during trials and protection of rights, safety and well being of trial subjects.

32. GOOD PHARMACEUTICAL PRACTICE 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 self-care and prescribing as well as use of medicines and other associated activities.

33. 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.

34. MARKETING AUTHORISATION HOLDER is a legal person that has been granted a marketing authorization for a given medicinal product in accordance with this Law. It may be a manufacturer with a registered office in the R of Macedonia or a legal person acting on behalf of manufacturer with a registered office in the R of Macedonia.

35. ADVERSE REACTION TO MEDICINAL PRODUCT is any unintended and noxious response to medicinal product, regardless of its dosage, which occurs at proscribed usage of medicinal product.

36. 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.

37. UNEXPECTED ADVERSE REACTION TO MEDICINAL PRODUCT is any unexpected and adverse reaction the outcome of which is not consistent with the summary of product characteristics.

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

39. 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.

40. 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 responsible authority.

41. MEDICAL DEVICE, shall mean any instrument, apparatus, accessories, 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
- diagnosos, 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. articles intended by their manufacturers to be used together with a medical device to enable its use,
2. articles 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. articles intended for clinical trials.

42. 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

43. CERTIFICATE ON CONFORMITY OF MEDICAL DEVICE is a certificate guaranteeing that the medical device complies with the basic requirements laid down by this Law. The certificate may be, depending on the classe of medical device concerned, issued either by the manufacturer or by Notified body in the EU or authorised body in the R of Macedonia

44. INSTITUTION FOR ASSESSMENT OF CONFORMITY OF MEDICAL DEVICE is a legal entity, independent from manufacturer/supplier and

authorized by Minister of the Economy and Minister of Health to assess conformity of medical device with the basic, i.e. general and specific requirements laid down by this Law.

45. SPONSOR of clinical trial is a company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial

46.MATERIOVIGILANCE

II. COMPETENT AUTHORITY

Article 3

An Agency for medicinal products shall be established for performing activities regarding the medicinal products and medical devices (herein after Agency) as authority within the Ministry of Health competent for the activities in this area. The Agency shall have a status of legal entity.

Article 4

The Agency shall be managed by a director.

The Director of the Agency shall be appointed by Government following the proposal of Minister of health

Criteria for the appointment of the Director shall include a university degree in the field of pharmacy and at least 10 years of relevant work experience including 5 years of relevant experience in management.

Article 5

Scope of the activities 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 authorisations 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;
6. maintaining Register of medical devices of the Republic of Macedonia;
7. maintaining Register of manufacturers of medical devices of RM;
8. maintaining Register of entities for wholesale and retail sale of medical devices of RM;
9. authorizations and/or reports for clinical trials of medicinal products;
10. notifications for clinical trials of medical devices;
11. issuing import authorizations for medicinal products;
12. issuing certificates for compliance with the good practices;
13. classification of products as medicinal products or medical devices;
14. establishing and maintaining farmacovigilence and materiovigilence system;
15. establishing and maintaining database;
16. inspection of medicinal products and medical devices;
17. inspection of entities for production, wholesale and retailing;
18. activities pertaining to assure control of the quality of the medicinal products and medical devices;
19. activities pertaining to assure implementation of pricing policy for medicinal products;
20. selecting and processing statistical data on the consumption of medicinal products and medical devices;
21. cooperation with other institutions on promotion of rational use of medicinal products and medical devices;
22. integration into international networks of information on medicinal products and medical devices;
23. undertaking other activities pertaining to medicinal products or medical devices in accordance with this Law.

Article 6

The National Laboratory for Control of Medicinal Products shall be the organization appointed by the Minister of Health for activities of analytical investigation of the medicinal products and quality control of the medicinal products.

Article 7

The Minister of Health, with consent of the Director of the Agency, 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.

The members of the committees should possess an university degree in medicine, pharmacy or dentistry and at least 10 year experience in the relevant field.

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 conflict of interests.

Article 8

The following Standing committees shall be established:
- Medicinal Products Committee;
- Traditional Herbal Medicinal Products and homeopathic medicinal products Committee;
- Medical Devices Committee;
- Clinical Trials Committee for medicinal products and medical devices;
- Pricing Committee.

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, prescribed by the Agency.

The committees shall be professionally independent within their scope of activities.

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

Article 9

The Minister of Health shall, having secured the approval of the Director of the Agency, establish a list of external 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.

In cases of doubt, where taking into account its characteristics, a product may fall within the definition of a medicinal product and within a definition of a product covered by other legislation, the provisions of this Law shall apply

Article 11

Medicinal product can be placed on the market provided that:
- marketing authorisation or parallel import authorisation was issued by the Agency pursuant to the procedures prescribed by this Law and its by-laws
- import authorisation was issued by the Agency for pursuant to the procedures prescribed in the the Law
- medicinal product is used for testing or clinical trials providing that notification or authorisation of clinical trial was issued by the Agency or
- Quality control of medicinal products has been performed in line with the Law

Nothwithstanding the provisions of the previous paragraph, medicinal product 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 an authorised medicinal product. The medicinal product concerned must either be subject of an application for marketing authorisation 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") in pharmacies
- medicinal products used only in medical institutions for the purpose of providing medical services

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

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

The Minister of health shall determine in greater detail the manner and procedure of classifying medicinal products according to the method and place of their dispensing.

Article 14

If medicinal product, already classified to be dispensed only on prescription, is on the basis of submitted significant preclinical tests or clinical trials reclassified to be dispensed over the counter, the Agency will not, for the purpose of evaluation other applicant's application, refer to the results of the submitted tests or trials one year form the authorisation of the reclassification,

Article 15

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

Marketing authorisation holder and medical professionals are not responsible for consequences of treatment that was not in line with issued marketing authorisation or for consequences of treatment with non-authorised medicinal product if the treatment was recommended or requested by the Agency or

Ministry of health in the cases of exceptional situations concerning public health protection.

Marketing authorisation holder has together with wholesaler of the medicinal products public service obligation e.g. obligation to guarantee permanently an adequate range of medicinal products to meet requirements for supply with the medicinal product within a very short period of time.

Article 16

Medicinal products marketed in the Republic of Macedonia must be manufactured and controlled according to the requirements of the European Pharmacopoeia and the national supplement thereof if prescribed by the minister in charge of health.

Should in the European pharmacopoeia and in the national supplement thereof not prescribe methods of manufacture and requirements concerning quality, medicinal products may be manufactured and controlled according to methods and requirements of other acknowledged pharmacopoeias or according to the methods proposed by the manufacturer.

III-A MARKETING AUTHORISATION OF MEDICINAL PRODUCT

Article 17

No medicinal product can be placed on the market unless a marketing authorisation has been issued by the Agency in accordance with this law.

Notwithstanding the provisions of the previous paragraph, a marketing authorisation 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 regulated by the Law in the Chapter on pharmacies
- galenic products regulated by the Law in the Chapter on pharmacies
- radiopharmaceuticals prepared at the time of use by a person or by an established authorised for use such a medicinal product from authorised

radionuclide generators, kits or radionuclide precursors in accordance with the manufacturer's instruction
- for medicinal products for which import licence has been granted on the basis of Art.79 of the Law.
- medicinal products provided as a donation according the Law

Article 18

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

The following persons can apply:
- manufacturers of medicinal products with a registered office in the Republic of Macedonia
- legal representatives of manufacturers respectively legal entities acting on behalf of manufacturers, with 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 or subsidiaries of foreign manufacturers with registered office in the Republic of Macedonia stipulating their valid insurance covers territory of the Republic of Macedonia.

Article 19

Applicant will be a marketing authorisation holder

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

Marketing authorisation 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.

Person responsible for pharmacovigilance must have university degree in human medicine or pharmacy.

Article 20

The marketing authorisation application shall contain at least the following components:

1. administrative component of documentation containing
   - information on the medicinal product
   - information on manufacturer, information on production sites, manufacturing authorisation based on fulfilling requirements of good manufacturing practice (issued 3 years ago max.)
   - information on future marketing authorisation holder for the medicinal product
   - proposed summary of product characteristics
   - proposed patient information leaflet
   - proposed packaging,
   - list of countries that have already authorised marketing of the medicinal product and list of countries in which the application was submitted, refused 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-biological component of documentation containing information on medicinal product quality: its qualitative and quantitative particulars, description of manufacturing methods, 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-foetal toxicity, mutagenic and carcinogenic potential, data on local tolerance, excretion and other data necessary for public health protection

4. Clinical component of documentation i.e. 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 authorisation in other countries

Article 21

The applicant is responsible for the authenticity of the submitted data

Documentation is to be provided in Macedonian or English language, except summary of product characteristics and patient information leaflet that are to be provided in Macedonian language.

Documentation enclosed in the application for authorisation of medicinal product is in the property of the applicant, is archived with the Agency and considered confidential with the exception of summary of product characteristics, and patient information leaflet that can be accessible to health care professionals or publicly accessible if so decided by the Agency.

Article 22

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

1. that exact bibliographic data on pharmacological-toxicological tests and clinical trials are taken over from published scientific literature and contain all information required in Art 20 para 1, items 3 and 4, provided that the substance in the medicinal product is well established, respectively that 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 other countries with equal standards for product quality, safety and efficacy

or

2. that medicinal product concerned is a generic of a reference medicinal product that has already been authorised for at least eight years in the Republic of Macedonia, EU or other countries with equal standards for product quality, safety and efficacy, provided that the Agency may issue a marketing authorisation only after the lapse of at least ten years from the issuance of the marketing authorisation 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 authorisation holder obtains an authorisation for one or more new therapeutic indications which, during the evaluation prior to their authorisation, 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 authorised active substance must be supplied by the applicant. The varous 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 active substances therapeutic indications, strength, pharmaceutical form or route of administration, vis-à-vis the reference medicinal product the results of appropriate pre-clinical tests or clinical trials shall be provided.

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(2), 23 and 24 of the Law, and the consequential practical requirements shall

not be regarded as contrary to patent rights or to supplementary protection certificate for medicinal product.

Article 27

In the case of medicinal product containing active substance used in the composition of authorised 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 Art 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 authorisation, the marketing authorisation holder may allow use to be made of the pharmaceutical, pre-clinical and clinical 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 authorisation shall be submitted to the Agency for every pharmaceutical form, strength and size of packaging of the medicinal product.

Within not more than 210 days from the receipt of a complete application for a marketing authorisation, the Agency shall decide to approve or to reject the requested marketing authorisation based on the documentation submitted and advice of the Medicinal Products Committee of the product quality, safety and efficacy.

The time limit referred to in para 1 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 or "clock stop" shall last until the request of the Agency has been met. This includes also a requested GMP inspection of a production site or GCP inspection of clinical trials presented, if so decided by the Agency.

Article 30

The marketing authorisation shall be issued for the period of five years.

The Agency shall reject issuing a marketing authorisation should the assessment of the provided documents demonstrate the following occurrences:
- that the risk.benefit ratio is unfavourable
- that the product quality, safety and or efficacy is 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, labelling or patients information leaflet is inconsistent with this Law and its by-laws
- that any particulars supporting the marketing authorisation application are incorrect or inconsistent with the Law.

Article 31

Notwithstanding the provisions of para 1 and second item of para 2 of article 30, in the exceptional cases of objective and justifiable reasons concerning public health, a marketing authorisation may be issued for the period of 1 year if issued under special conditions including obligation to provide additional proof of safety and efficacy and measures taken and to report them annually for the purpose of renewal of the marketing authorisation.

Constituent part of a marketing authorisation shall be approved summary of product characteristics, patient information leaflet and packaging mock up or specimen.

Summary of product characteristics from the para (2) of this Article shall contain at least the basic information on the medicinal product (name, generic name, qualitative and quantitative particulars, pharmaceutical form, strength, size of packaging, marketing authorisation 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 para (2) of this Article shall contain all necessary data in line with Art.84 and 85 of the Law.

Article 32

Contents of the application, the procedure and the requirements for obtaining a marketing authorisation, the form and contents of the required documentation and conditions for recognition of marketing authorisation issued in the EU, condition for obtaining a conditional marketing authorisation as well as fees to be paid shall be prescribed in greater details by Minister of health

Article 33

A marketing authorization shall cease to be valid:

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

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

3. if the Agency revokes, withdraw suspend or vary the marketing authorisation provided that:

- the medicinal product has been marketed contrary to the marketing authorization
- the medicinal product has been marketed contrary to this Law and/or its by-laws
- the medicinal product is harmful under the prescribed conditions for use;
- the medicinal product does not have favourable benefit - risk 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 authorisation authorisation;
- 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.

- if any particulars supporting the marketing authorisation 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 34

A medicinal product whose marketing authorization has expired and has not been renewed within the time period defined 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 35

Should the manufacturer decide to cease manufacturing or marketing of a medicinal product before the expiry of the marketing authorization, it shall report it to the Agency at least six (6) months before ceasing manufacturing or marketing of the medicinal product.

Article 36

The marketing authorisation may be renewed after five years on the basis of re-evaluation of the risk-benefit ratio by the Agency.

For the purpose of renewal of marketing authorisation, the marketing authorisation holder shall submit the application to the Agency. at least six month before the marketing authorisation ceases to be valid. The appllication shall contain a consolidated version of the file in respect of quality, safety and efficacy, including all variations introduced since the marketing authorisation was granted, Consolidated version of the file shall contain 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 to re-evaluate the risk-benefit balance.

Within not more than ninety (90) days from the receipt of a complete application for a marketing authorisation, the Agency shall decide to approve or to reject the requested renewal of marketing authorisation based on the documentation submitted and Medicinal Products Committee's re-evaluation of the product's risk.benefit ratio.

The time limit referred of 90 days 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 or "clock stop" shall last until the request of the Agency has been met.

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

Minister of health shall prescribe in greater details the procedure of and conditions for the renewal of a marketing authorization, form and contents of the required documentation as well as fees to be paid.

Article 37

The marketing authorization holder shall follow all scientific and technical developments related to the authorised medicinal product, shall take into account findings concerning product's quality, safety and efficacy and 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 that may influence variation of the marketing authorisation or change of its marketing authorisation documentation shall be notified with or applied to the Agency.

Article 38

The marketing authorization holder shall regularly notify the Agency of all smaller changes of types IA and IB in the documentation, i.e. marketing authorization, introducing the changes only if the Agency fails to give a negative opinion on them within thirty (30) days from their notification, which shall contain all necessary documents concerning the change.

Article 39

To introduce major changes of type II in the marketing authorization, 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 (60) days from the receipt of a complete application, in the form of decision.

The time limit of sixty days 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 40

In the case of the extension of the existing application to changes that concern active substance, pharmaceutical form, strength or new indication field, a new application is required provided that the reference to the already submitted parts of documentation is accepted. The procedure followed is as for a new marketing authorisation.

Article 41

Minister of health shall prescribe in greater details the form and the content content of application/notification and procedure for notification or approval of the changes of marketing authorisation or already provided documentation as well as fees to be paid.

Article 42

For traditional herbal medicinal products a simplified registration procedure is established and at least following documentation is to be provided:
1. administrative component of documentation according to Art 20 para (1) point 1 of the Law
2. pharmaceutical-chemical-biological documentation according to Art 20 para (1) point 2 of the Law
3. bibliographic or expert evidence to the effect that the medicinal product in question, or a correspodenting product has ben in medicinal use through a period of at least 30 years including at least 15 years in R of Macedonia or in the EU or countries with the same level of requirements for quality ans safety of those products.
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 procedure and the requirements for obtaining a registration for traditional herbal medicinal products and the form, contents of the required documentation and conditions for recognition of marketing authorisation issued in the EU as well as fees to be paid shall be prescribed in greater details by Minister of health

Article 43

The Agency shall reject issuing a marketing authorisation for traditional herbal medicinal product should the assessment of the provided documents demonstrate the following occurrences:
- that therapeutic indications do not comply with the conditions requested in the Law for traditional herbal medicines
- 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 44

For homeopatic medicinal products a simplified registration procedure is established if provided that:
1. they are administered orraly or externally
2. no specific therapeutic indication appears on the labelling of the medicinal product or in any information relating thereto
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 mother tincture or more than 1/100th 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 medical prescription.

Contents of the application, the procedure and the requirements for obtaining a registration for homeopathic medicinal products, the form and contents of the required documentation, conditions for advertising and labelling of the products, conditions for recognition of marketing authorisation issued in the EU as well as fees to be paid shall be prescribed in greater details by Minister of health

Article 45

Minister of health may determine a list of essential medicinal products necessary for performing the health care.

Article 46

Minister of health may, provided that probability for clinically significant differences in safety and/or efficacy is neglectible or low, prescribe the manner and procedure for substitution of medicinal products in pharmacies.

Minister of health shall prescribe in greater details the manner and procedure for substitutionof medicinal products in pharmacies.

Article 47

List of medicinal products for which the marketing authorisation was issued by the Agency and list of medicinal products for which the marketing authorisation was rejected, changed, withdrawn, sispended or temporarly suspended shall be published in the Official Journal of the R of Macedonia.

Minister of health shall prescribe in greater details the content of the information to be published in the Official Journal of the R of Macedonia.

Article 48

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

Minister of health shall prescribe in greater details the procedure for transfer of marketing authorisation, content of documentation to be submitted and procedure for verification of prescribed conditions and other requested data as well as fees to be paid.

III B 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 which confirm its quality, safety and efficacy.

A medicinal product may undergo analytical, pharmacological-toxicological tests and clinical trials even if it has already been granted a marketing authorisation, with the purpose of obtaioning additional information on the medicinal product or its control.

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

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

Article 50

Analytical and 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 other requirements and principles of good practices and are authorised by Minister of health for those activities.

Data on analytical and pharmacological-toxicological tests and clinical trials are parts of documentation submitted for the purpose of obtaining marketing authorisation of medicinal product. They 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 such a way that tests and trials can be repeated and results compared.

Minister of health shall describe requirements for authorisation of medicinal products investigational institutions and the verification procedures as well as 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 good control laboratory practice, with 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, principles 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 complience 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 favourable or unfavourable.

Minister of health shall describe in detail manner, principles and procedures for pharmacologilal-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 and pharmacological-toxicological tests have been submitted and if trials are performed on medicinal product that does not influence the human germ line.

Clinical trials of medicinal products shall be performed in accordance with ethical principles of the Declaration of Helsinki and signed other 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.

Article 55

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 unerstandable to them and in writting.

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 applicant for clinical trials is the sponsor of the trial or his authorised representative.

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

Article 58

The applicant for a clinical trial of a medicinal product that has not yet received a marketing authorization in the R. of Macedonia, shall file a clinical trial application with the Agency prior to the clinical trial.

The application for clinical treals 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 trals already performed on

the investigational medicinal product, positive opinion of the National ethical Committee, information on investigational institution, investigators and other information necessary for decision on the approval or rejection of the trial.

The Agency shall decide to approve or to reject the clinical trial authorization within not more than sixty (60) days from the receipt of a complete application for the clinical trial on the basis of the opinion of the Committee for Clinical Trials .

The time limit of 60 days 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.

The application for clinical treals 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 trals already performed on the investigational medicinal product, positive opinion of the Nathional ethic committee information on investigational institution, investigators and other information necessary for decision on the approval or rejection of the trial

Te Agency shall, within not more than thirty (30) days from the receipt of a complete notification for clinical trial inform the applicant of the reasons for rejecting the clinical trial.

The time of 30 days 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 (30) days, it may commence the clinical trial.

Article 60

Sponsor must notify with the Agency all relevant changes of the clinical trials

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

Article 61

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

Article 62

The Agency shall supervise the conduct of clinical trilas in accordance with the Law, its by-laws and guidance for good cilnical 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 in greater details the manner, principles and procedure for clinical trials, content of documentation to be submitted and procedure as well as fees to be paid.

III C MANUFACTURING OF MEDICINAL PRODUCTS

Article 65

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

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

Manufacturing licence allowes also the sale of the manufactured medicinal product from manufacturer to wholesalers.

Manufacturing licence can be required for:
- manufacturing process as a whole or parts of manufacturing process
- particular production site (manufacturing place)
- particular pharmaceutical form
- manufacturing of row materials
- manufacturing of excipients if required by legislation (list may be issued by Agency)

Manufacturing licence is required for importers for parts of manufacturing process to be performed by importer (e.g.packaging, repackaging, labelling, introducing patient information leaflets etc)

Article 66

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

Manufacturer of radiopharmaceutical medicinal products must ensure that that raw material for the products comply with conditions determined by a special law

Article 67

The manufacture of galenic preparations produced in galenic laboratory of an authorised pharmacy up to 100 finished packages per day shall not be considered manufacture of medicinal products under this Law and shall be carried out in galenic laboratory of the authorised pharmacy complying with the provisions of the Law on pharmacies.

Article 68

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 and guidelines 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, chemical technology, medicine, stomatology 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 additional knowledge in medicinal products testing 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 authorisation.
- manufacturing process must be performed in line with principles and guidelines of good manufacturing practice
- raw materials used as active substances shall be produced in line with good manufacturing practice. This shall apply also to those excipients for wich it is required by legislation.
- to manufacture only tose medicinal products covered by the granted manufacturing authorisation and in compliance with granted marketing authorisation for the medicinal products.
- to introduce a quality system in accordance with good manufacturing practice
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Article 69

The application for manufacturing licence shall contain proof of fulfilling conditions defined in Art 79 and shall be submitted to the Agency

The Agency shall within ninety (90) days from the receipt of complete application, approve or reject the application for manufacturing licence on the basis of submitted documentation and results of the inspection performed.

The time limit of 90 days 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.

Manufacturing licence shall be isued without a time limit.

Article 70

The manufacturer shall notify the Agency about any changes concerning the conditions defined in Art 68 on the basis of which the manufacturing licence has been granted.

Te Agency shall, within not more than thirty (30) 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 production site

The time of 30 or 90 days 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 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 licence shall be suspended or revoked should the Agency that the manufacture of medicinal products no longer satisfies the requirements defined in the Law and its by-laws

Contents of the application, the procedure and the requirements for obtaining a manufacturing licence, as well as fees to be paid shall be prescribed in greater details by Minister of health

III D MARKETING OF MEDICINAL PRODUCTS

Article 72

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

Legal entities involved into marketing of medicinal products and marketing authorisation holders shall, on request of the Agency, 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 and sale of medicinal product.

Wholesale distribution of medicinal product may only be carried out by legal persons holding a licence for wholesale distribution of medicinal products issued by the Agency

Wholesalers shall be allowed to purchase medicinal products from legal persons that hold the licence for manufacturing or wholesale distribution of medicinal products and to sell to legal persons that hold the licence for wholesale or retailsale of medicinal products

Wholesalers shall be allowed to purchase, sell or distribute for free, only medicinal products for which a marketing aouthorisation or import authorisation was granted or investigational medicinal products for approved or notified clinical trials as well as medicinal product designed for further manufacturing only.

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 and storage corresponding to the quantity and type of medicinal products that are subject to marketing
- to have employeed or otherwise contracted an adequate number of professionals holding university degree in pharmacy and other suitable profiles and with an additional appropriate education concerning the wholesale
- to have employed a person responsible for receiving, storage, 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 additional knowledge in medicinal products testing and shall be permanently and continuously at disposal.
- to keep appropriate documentation so as to enable 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 organised 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 of a specific geographical area and to deliver the supplies requested within a very short period of time over the whole area in question.

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Article 75

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

Notwithstanding the provision of the previous paragraph, importer may enter into an agreement Official Medical Control Laboratory to provide the abovementioned control on their behalf.

Agency may recognise batch analyses signed by qualified person of some other countries Official Medical Control Laboratory (OMCL) or of a manufacturer in the EU or in other countries with equal standards for issuing manufacturing licence as in the R of Macedonia providing that specific conditions concerning requirements for recognition of other OMCLs or manufacturers are fulfilled.

Importers that perform parts of manufacturing process (e.g.packaging, repackaging, labelling, introducing patient information leaflets etc) must have in addition to wholesale licence, a manufacturing licence for the processes performed.

Article 76

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

The Agency shall within ninety (90) days from the receipt of complete application, approve or reject the application for wholesale licence on the basis of submitted documentation and results of the inspection performed.

The time limit of 90 days 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.

Wholesale licence shall be isued without a time limit.

Article 77

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

Te Agency shall, within not more than thirty (30) 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 of 30 or 90 days 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 78

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

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

Wholesale licence shall be suspended or revoked should the Agency that the wholesaler of medicinal products no longer satisfies the requirements defined in the Law and its by-laws

Contents of the application, the procedure and the requirements for obtaining a wholesale licence, conditions for recognition of other laboratories batch analysis, as well as fees to be paid shall be prescribed in greater details by Minister of health

Article 79

Import of medicinal products that have a marketing authorisation, parallel import licence, clinical trials licence or notification is free providing that requirements defined by the Law are fulfilled.

Notwithstanding the provision of the previous paragraph, the Agency shall issue an authorisation for import of medicinal products in the following situations:

- the medicinal product is on the essential list of products for which a marketing authorisation 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 authorisation was granted
- the medicinal product is required by a hospital or other health institution for treating individual patient or group of patients
- the medicinal product is needed for continuation of treatment that has been started aboard
- 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
- the medicinal product is used for pre-clinical testing of a medicinal product
- medicinal product is designated for further manufacturing only

Article 80

The applicant for obtaining an authorisation for import of medicinal products is importer

The application for obtaining an authorisation for import of medicinal product shall contain proof of fulfilling conditions defined in Art 79 and shall be submitted to the Agency
Te Agency shall, within not more than thirty (30) days from the receipt of a complete application approve or reject it.

The time of 30 days 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.

Contents of the application, the procedure and the requirements for obtaining an authorisation for import of medicinal product, as well as fees to be paid shall be prescribed in greater details by Minister of health

Article 81

Medicinal products are to be retailed in pharmacies.

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

Pharmacies is legal entity.

Founder and person carrying out the work in pharmacy must be performed by a professional with high university degree in pharmacy and granted working licence.

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

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 quality 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 5th degree in pharmacy;
- to keep appropriate documentation as to enable monitoring the despensing of medicinal products;
- to have introduced quality system and organised 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 geografical area

Pharmacies shall meet the requirements for preparing, control and despense magistral medicinal products and dispensing galenic products.

All provisions concerning pharmacies shall apply also to e-pharmacies.

Minister of health shall describe in details manner, principles and procedures for authorising pharmacies and e-pharmacies, until The Law for Pharmacies is established.
Minister of health shall issue a guideline on Good pharmaceutical practice

III E LABELLING AND PATIENT INFORMATION LEAFLET

Article 83

Information on each medicinal product placed on the market must be written in the Macedonian language 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 generic 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, medicinal product batch number, marketing authorization number and other relevant identification codes, different warnings, and other relevant information.

Name of medicinal product must be written on its outer package also in Braille letter (see transitional provisions)

The inner packing must contain at the least the basic information on the medicinal product (name and generic name, qualitative and quantitative particulars of the active substance, medicinal product form, strength), manufacturer/marketing authorization holder, date of expiry, medicinal product batch number and other relevant information, if so 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 Macedonial language in line with summary of products characteristics, unless all the information required by the Law and its by-laws 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, generic 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 authorisation holder must, if required by patient organisations, ensure patient information leaflet appropriate for blind or weak-eyed patients provided to them properly.

Article 85

As an exception of article 83 of the Law, in exceptional cases, 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 that patient information leaflet in Macedonian language is provided to patients properly.

Article 86

Contents of the outer and inner package, the structure and the content of patient information leaflet and procedure and criteria for exceptions shall be prescribed in greater details by Minister of health

III F PHARMACOVIGILANCE

Article 87

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

Minister of health may authorise a legal person for collection and evaluation of adverse reactions or events, information about intereactions or abuse of medicinal products as well as for advicing the Agency on measures to be taken, if necessary.

Article 88

Medical professionals shall be obliged to notify with a legal person from the second paragraph of this Article about any adverse reaction or events or suspicious of them in accordance with the Law and its by-laws.

Article 89

Marketing authorisation holders shall be obliged to notify immediately with the legal person from the second paragraph of Article 87 and the Agency about any serious adverse reaction or events or suspicious of them that occured in the R of Macedonia or other countries.

Marketing authorisation holders shall be obliged to submit periodical safety updated reports to the Agency either in the set time periods or upon request by the Agency.

Article 90

Minister of health shall prescribe in more great detatils the manner and procedure of reporting adverse reactions or events, manner of reacting to them, duties of medical professionals, marketing authorisation holders and the legal person from the second paragraph of this Article, manner of reporting and

contents of periodical safety updated reports and manner of organisation of the system of pharmacovigilance.

III G 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 medicinal product, labeled as being "free of charge and not for sale", except medicinal products containing narcotic substances.

Article 93

Marketing authorization holders or legal and physical persons acting on their behalf shall not offer direct or indirect financial benefit to persons who prescribe or dispense medicinal products.

Marketing authorization holders may enable persons prescribing or dispensing medicinal products to acquire additional knowledge on new medicinal products and already marketed medicinal products.

The acquisition of knowledge referred to in the previous paragraph 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 objectively inform the public about the medicinal product characteristics in line with summary of product characteristics or patient information leaflet, unless otherwise decided by the Agency.

Article 95

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

Notwithstanding 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, war state and other extraordinary situations), 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 requirements and manner of advertising of medicinal products.

Article 97

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

1. by an announcement in the official gazettes of the R of Macedonia;
2. by publishing a register of medicinal products in the R of Macedonia in the manner allowing its availability to health care professionals
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 H QUALITY CONTROL OF MEDICINAL PRODUCTS

Article 98

Quality control of medicinal products shall be aimed to ensure that medicinal produsts 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 deetermine conformity of medicinal product's quality with the marketing authorization requirements.

Article 99

Quality control of medicinal products shall be performed by Official medical control laboratory(ies) appointed by Minister of health among acredited laboratories.

Medicinal product quality control 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 proven analytical methods

Minister of health shall determine the national supplement of Ph.Eur that shall be published in the Official Gazette of the R of Macedonia

Article 100

Quality control of medicinal products shall refer to the following:

1. Regular quality control of all medicinal products marketed in the R of Macedonia, carried out at least once in every five (5) years;
2. Quality control of the first medicinal product batch, carried out before marketing of the medicinal product;
3. Quality control of every batch of manufactured, i.e. imported medicinal products or paralelly imported 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 licence or after their issuance;
5. Specific quality control, i.e. control of every batch of specific categories of medicinal products (e.g. immunologicals, medicinal products derived from blood) if required by the Agency

Article 101

Medicinal product quality control shall be carried out by the Official medical control laboratory upon proposal by:

1. the Agency;
2. importers, except in the case referred to in Article 75 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 Official medical control laboratory shall issue a certificate on the product quality control results, i.e. report them to the Agency, customer and marketing authorization holder.

Article 102

Expences for samples and quality control shall be paid by:

- marketing authorization holder, for regulat quality control, quality control of the first medicinal product batch after marketing authorization or parallel import authorisation, specific quality control, i.e. control of every batch of specific categories of medicinal products (e.g. immunologicals, medicinal products derived from blood), quality control of every batch of imported medicinal products, extraordinary medicinal product quality control, if demonstrated that the quality of a medicinal product is not in conformity with the provisions of the marketing authorization or 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 art 101 of the Law.

Article 103

The manner, content and procedure of quality control of medicinal products, carried out by the authorized control laboratory for the quality control purposes, conditions for recognising analytical control performed by other laboratories, method of sampling and expences for quality control as well as the method of keeping evidence, shall be prescribed in greater details by the Minister of health

Article 104

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

Manufacturers, wholesalers/importers, retailers or marketing authorisation holders shall inform the Agency and other relevant stakeholders about quality defect or any other incomplience that could compromise public health.

Marketing authorisation holder/importer shall withdraw the concerned product from the market and perform other activities necessary for protection of health and immediatelly inform the Agency about all actions taken.

Agency shall monitor all activities of the marketing authorisation holder/importer, intervene and report into the international rapid alert sistem if necessary for the purpose of protection of health

III I DONATIONS OF HUMANITARIAN ORIGIN

Article 105

Medicinal products of humanitarian origin shall be imported to and used in the R of Macedonia 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 of humanitarian origin and free of charge.

The following requirements shall be met to obtain an authorization for import of medicinal products foreseen as humanitarian aid:

1. that 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 duration,
2. that the offered medicinal product type and quantity is needed to the system of health protection, and
3. that there is at least one (1) year left until the expiry of the medicinal product.

Medicinal products of humanitarian origin, imported to the R of Macedonia contrary to the provisions of this Law, shall be returned to the sender, i.e. disposed of at its expense.

The Miniser of health shall ensure an oversight over the equipment, storage and distribution of medicinal products of humanitarian origin.

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 wrapping, i.e. packing has been damaged,
4. that laboratory control has demonstrated that it does not conform to the required 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 lives 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 J PRICING

Article 107

Prices of medicinal products are formed freely, except in cases prescribed by the Law

To ensure better availability and supply of medicinal products for protection of health in the R of Macedonia, Minister of health, shall regulate medicinal product prices in one or more of the following manner:

1. prices of medicinal products that are covered by public fund and have either marketing authorization, parallel import authorization or import authorization for product on the essential list of medicinal products for which a marketing authorisation has not been issued shall be formed and controlled in the manner prescribed by Minister of health at any level of marketing (e.g. manufacture, wholesale, retail)

2. marketing authorization holders, parallel import authorization holders or importers of non-authorised products of product being on the essential list of medicinal products shall provide the Agency with all relevant data necessary for forming and controlling prices of medicinal products.

3. medicinal products that are covered by public fund can only be marketed if the price is formed in accordance with criteria prescribed by Minister of health.

Article 108

The price regulation of medicinal products shall satisfy the following criteria:

- it shall not be discriminatory

- it shall not allow mechanism of dumping

- it shall be formed upon application of marketing authorization holders, parallel import authorization holders or importers/manufacturers of product being on the essential list of medicinal products for which a marketing authorisation has not been issued and approved by the Agency within 90 days from the acceptance of completed application.

- it shall include the appeal mechanism

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 shall sell medicinal products only at a price formed in accordance with the Law and its by-law.

Prices of medicinal products purchased by tender can be reduced according to the tender rules and law.

The method of determining/forming prices of medicinal products, method of price control and method of reporting medicinal product prices shall be prescribed in more detail by the Minister of health

IV MEDICAL DEVICES

IV A 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 higher risk potential,
3. Class II-b – medical devices with a high 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 only in pharmacies and specialized stores,
2. medical devices dispensed without prescription/order only in pharmacies and specialized stores,
3. medical devices dispensed on prescription/order 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-B ESSENTIAL, GENERAL AND SPECIFIC, REQUIREMENTS FOR MEDICAL DEVICES

Article 116

Medical devices must be in accordance with the requirements concerning general safety of products and must meet essential requirements that are divided into general and specific.

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 shall mean requirements that medical devices must meet in order to be used for the original purpose.

Essential requirements, i.e. general and specific requirements that medical devices must meet shall be prescribed in detail by the Minister of health

IV C MEDICAL DEVICES CONFORMITY ASSESSMENT

Article 117

The procedure for assessing conformity of medical devices with the general and specific requirements referred to in 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 and its by-laws.

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. certificate 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 sterility of measuring function;
2. for medical devices of classes II-a, II-b and III, conformity assessment with the general and specific requirements, as well as the oversight over the quality system shall be performed by authorized institutions.

Article 118

Conformity assessment procedure shall be performed:

- by conformity assessment authority recognized in the EU e.g. Notified Body

or

- by institution authorized by Minister of the Economy and 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

Notwithstanding the provision of paragraph 1 of this Article, if it concerns public health, conformity of medical device with essential general and specific requirements may be assessed by the Commission for Medical Devices on the basis of submitted documentation supporting the product.

Content of the requests and procedure for assessment of conformity of certain types of medical devices with the general and specific requirements as defined the Laws and its by-laws, and contents of the conformity assessment certificate of medical devices shall be prescribed in greater details by the Minister of health

Minister of Economy shall prescribe requirements concerning premises, equipment and staff that are to be met by the institutions dealing with conformity assessments of certain types of medical devices,

IV D 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 conformity mark used in the R of Macedonia and the contents of the conformity certificate issued in the R of Macedonia shall be prescribed by the Minister of the Economy unless otherwise regulated by a special law.

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 e.g. Notified Body in the EU, shall mark the medical device with the CE mark that is recognized in the R of Macedonia. Manufacturer of medicinal devices belonging to Class I may mark his product with CE mark if based on the statement/certification that the product meets the requirements of the Law e.g. is in conformity with the general and specific requirements.

It shall be forbidden to mark a medical device with the mark referred to in this Article, if such marking is inconsistent with the Law and its by-laws

Notwithstanding the provision of the previous paragraph, Minister of health may, in the exceptional cases of objective and justifiable reasons concerning public health allow marketing of limited amount of specific medical devices that are not marked in line with provisions of the Law.

Article 120

Notwithstanding the provision of the previous Article it shall not be necessary to mark medical devices that are:

1. intended for clinical trials,
2. custom made medical devices.

IV E 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 entered in the Register of manufacurers of medical devices in the R 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 employeed or otherwise contracted an adequate number of professionals of suitable profiles and with an additional appropriate education concerning the manufacturing
4. that they have an employee with, at least, the 6^{th} degree in a medical field should she/he be responsible for medical devices of classes I and II and with the 7^{th} degree in a medical field should she/he be responsible for medical devices of class III, who is in charge of monitoring and reporting undesirable effects and reactions according to the provisions of the Law,
5. that they have a liability insurance for any damage caused to the user or a third person.
6. that they produce only medical devices in conformity with the prescribed general and specific requirements referred to in the Law and properly marked

.

In accordance with this Law, 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 observe technical regulations in the process of manufacturing medical devices to ensure their conformity with the general and specific requirements.

A technical regulation may state that a medical device is considered to be in conformity with the technical regulation requirements if it meets the requirements of non-mandatory recognized standards that the technical regulation refers to.

Article 123

Notification for manufacture of medical devices in the R of Macedonia shall contain the documents proving that requirements listed in Art 121 were fulfilled, together with the following information:

- address of the manufacturer and confirmation of registration on court

- list of medical devices that will be manufactured and their classification

- documentation demonstrating that the medical devices shall be manufactured in a manner ensuring the quality system provision and the public health protection, and in accordance with the essential, general and specific, requirements.

- documentation concerning the design, quality control and maintenance method of the medical devices.

Agency shall within ninety (90) days inform the manufacturer about entering into the Register of manufacturers of medical devices in the R of Macedonia.

The time of 90 days shall be suspended on the day when the Agency requests the manufacturer 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.

Manufacturers of medical devices registered in the R 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 or natural persons registered for the wholesale activities

Minister of health shall prescribe in greater details the contents, and the form of documentation to be submitted for notification 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 supplier/importer of the medical device in the R of Macedonia

IV F MARKETING OF MEDICAL DEVICES

Article 125

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

Article 126

Wholesale distribution of medical devices shall include purchase, storage, transport supply and and sale of medical devices, as well as their import and export, except dispensation of medical devices to individual users

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

Wholesalers of medical devices shall be allowed to purchase and sell only medical devisec that are in conformity with the prescribed essential, general and specific, requirements referred to in the Law and properly marked.

Wholesalers of medical devices shall be allowed to purchase and sell medical devices only to legal persons that have entered the registr+er of manufacturers, wholesalers or retail traders of medical devices in the R of Macedonia.

Article 127

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

7. 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 R of Macedonia
8. to have employeed or otherwise contracted an adequate number of professionals of suitable profiles and with an additional appropriate education concerning the wholesaling
9. The wholesale activity is carried out in a manner ensuring the implemented quality system and the public health protection,
10. they have an employee or otherwise contracted person who is in charge of monitoring and reporting undesirable effects and reactions according to the requirements of the Law,
11. that wholesaled medical devices are in conformity with the prescribed general and specific requirements referred to in the Law and properly marked

.

Article 128

Notification for wholesalers of medical devices in the R of Macedonia shall contain documents proving that conditions listed in the previous paragraph are met and the following documents:

- address of the wholesaler and confirmation of registration on court

- 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 in the R of Macedonia.

The time of 90 days shall be suspended on the day when the Agency requests the wholesaler 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.

Wholesalers of medical devices registered in the R 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.

Wholesaling shall also involve selling products to legal entities or natural persons registered for the retail trade activities

In accordance with this Law, requirements 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, transport and sale of medical devices to individual users

Medical devices may be retailed in pharmacies and/or specialised shops

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

Legal persons involved in retail trade with medical devices may purchase medical devices only from the medical devices wholesalers recorded in the register of wholesalers kept by by the Agency.

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

12. 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 specialised stores for medical devices in the R of Macedonia
13. that the activity is carried out in a manner ensuring the public health protection,
14. to have employeed or otherwise contracted an adequate number of professionals of suitable profiles and with an additional appropriate education concerning the retailsale in specialised stores
15. that they have an employee with, at least, the 5^{th} degree in a medical field should she/he be responsible for medical devices and in charge of monitoring and reporting undesirable effects and reactions to them,
16. that saled medical devices are 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 precious paragraph of this article, the Agency shall within ninety (90) days inform the applicant about entering into the Register of specialized shops of medical devices in the R of Macedonia.

The time of 90 days 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.

Specialised stores of medical devices registered in the R of Macedonia shall regularly update information submitted and shall report to the Agency all documentation or 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 specialised 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 and 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 previous paragraph, the availability of the data from the register as well as expenses associated with recording shall be prescribed by the Minister of health

IV G LABELLING OF MEDICAL DEVICES

Article 132

All medical devices marketed in the R of Macedonia must be labeled according with the provisions of the Law on the outer and inner packing in Macedonian language and must enclose instructions for use.

A packing of medical devices must contain, at least, the following: information on the manufacturer, i.e. supplier; information necessary for the identification of

the medical device and contents of the packing; different labels like "sterile", "custom-made", "single use", "for clinical trials", if necessary; identification code; expiry period; storage conditions; and, if required, a special method of use; warnings or precautions; 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 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 H CLINICAL TRIALS OF MEDICAL DEVICES

Article 133

Clinical trials of medical devices shall refer to establishing or confirming safety of medical devices, their usefullness 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 persons that meet the requirements pertaining to premises, equipment and staff, as well as other requirements and principles of good practices and are authorised 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 signed other 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.

All documents on clinical trials of medical devices must 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

essential, general and specific, requirements of this Law and the purpose defined by its manufacturer.

Before commencing clinical trials, legal persons carrying out and sponsoring clinical trials must insure themselves from the liability for any damage possibly caused to the investigational subjects in the course of clinical trials.

Article 134

Before commencing a clinical trial of a medical device in the R of Macedonia, the intended clinical trial of the medical device must be notified with the Agency.

The clinical trial can be notified by sponsor of the clinical trial or his 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 trals already performed on the device concerned or similar device, clinical trials protocol, positive opinion of the National ethics committee, inform 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 (2) 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 135

Sponsor must notify with the Agency all relevant changes of the clinical trials

If the sponsor 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 immediatelly inform the Agency, the National ethics committee and legal person from the second paragraph of article 151 of the 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 and its by-laws

Article 137

Required documentation and the procedure of notification of clinical trials, changes of notified clinical trials, reporting adverse reactions and events or incidents, requirements that shall be met by legal persons entitled to carry out clinical trials of medical devices, procedure of their verification and oversight as well as expences/fees assocates with the procedures shall be prescribed by the Minister of health

IV I MATERIOVIGILANCE

Article 138

The provisions of Article 87 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 manner and procedure 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, i.e. the system of materiovigilance.

IV J ADVERTISING OF MEDICAL DEVICES

Article 139

The provisions of Chapter III G 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 legal entities providing helath care services.

Minister of health shall prescribein great details the conditions for and manner of advertising medical devices to tp general and professional public

IV K DONATIONS OF HUMANITARIAN ORIGIN

Article 140

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

V INSPECTION

Article 141

Inspection of putting this Law and its by-laws into effect shall be carried out by a pharmaceutical inspection.

Notwithstanding provision of the previous paragraph, inspection of putting this Law and its by-laws cocncerning pricing of medicinal products shall be carried out by trade inspectors.

Notwithstanding provision of the paragraph 1, inspection of import of medicinal products is carried out by customs officers with expert support/help of the Agency

Article 142

Pharmaceutical inspector shall have an university degree in pharmacy, shall have passed an exam for Civil servant, to perform their activities in accordance with Law on administration procedure required for inspector, shall have minimum of

three (3) years of relevant experience and adequate annual training required for pharmaceutical inspectors.

Pharmaceutcal inspector with content of the Agency, may engage prominent 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

Pharmaceutical inspector shall be within his/her rights and obligations, independent

Article 143 (new)

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 (new)

The pharmaceutical inspector shall prove his/her official status with a 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 (new)

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.

Article 146

Pharmaceutical inspector shall, in addition to rights and obligations, have the following competence to:

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 entitiy to bring their operations in line with the requirements set out in the Law or its by-laws 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 unfavourable risk/benefit ratio under prescribed conditions for use
4. to order the destruction of a opposable/defective medicinal product in line with rules on environmental protection.
5. to ban the import of a medicinal products which has not been granted marketinng authorisation, parallel import authorisation or import authorisation granted by the Agency or which has been transported contrary to the manufactirer'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 take away (confiscate) medicinal products that are manufactured or marketed by legal persons not in possession of manufacturing or wholesale authorisation. Those legal persons are subject to offence, i.e. criminal act
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 which is inconsistent with this Law
10. to identify the violator of the provisions of this Law and acquire his personal data
11. to order discharge from the work the individuals that have not undergone checkups within the specified period, they should not be allowed to work in the manufacturing process and marketing with medicinal products and medical devices;
12. to order ban or temporary ban of clinical trial of medicinal product in the trial is not in line with thew Law

13. to order a temporary ban of retailsale up to 90 days and/or penal offences if they release other medicinal product instead of the prescribed if the replacement is not permitted, or if the manufactured medicament is not in the prescribed proportion;
14. to order other measures for which she/he is authorized by this Law and the by-laws enacted pursuant to the Law necessary for implementation of the Law and its by-laws

Article 147

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 goods, documents or samples for the purpose of protecting evidences and data, as well as to undertake other activities e.g. control of other relevant aspects concerning the staff in accordance with the purpose of the inspection oversight.

Pharmaceutical inspector shall have the right to enter the premises of manufacturers, their representatives, wholesalers, retailsales, and marketing authorisation holders regardless of official hours and 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 (new)

The license for work of the legal entity shall be revoked if an administrative measure stipulated in article 146 of this law, with a legally effective decision of the pharmaceutical inspector, is 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 Register.

Article 149 (new)

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 stipulated in paragraph 1 of this article which he/she banned from marketing.

Article 150

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

The pharmaceutical inspector may take a decision orally only, followed by written decision, 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 may order an immediate implementation of the oral decision.

The decision taken by the pharmaceutical inspector may be appealed against to the Agency within eight (8) days from the 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 authorisation for medicinal product not to place the medicinal product or to cease to supply the medicinal product due to its pricing, trade inspector can order marketing or further marketing of the products, if it would seriously jeopardise the supply of medicinal products and have negative consequences on public helath, for a period of maximum three (3) months.

Legal person responsible for price of the marketed medicinal product, that markets the products against provisions on pricing set up in the Law and its By-laws, shall 15 days after trade inspectors order bring the price of the medicinal product in line with the provision and to pay the difference between the two prices.

Trade inspector will inform the Agency on his decision.

Article 152 (new)

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 of this Law, which concern inspection, shall also be appropriately applied to medical devices.

Inspectors in charge for medical devices shall have the right and duty to propose initiating of petty offence proceedings, i.e. the right and duty to order or 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 the Law and the by-laws enacted pursuant to the Law 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 with the prescribed requirements,
4. to issue a 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 issue a temporary ban on marketing of a medical device that is inconsistent with the prescribed requirements or in other cases foreseen by this Law,
6. to temporarily ban the work of a legal person for the lack of conformity with the prescribed requirements
7. to take away (confiscate) medical devices that are manufactured or marketed by legal persons not entered in the register of manufacturers, wholesalers, pharmacies or specialised stores for medical devices kept by the Agency and as such are subject to offence, i.e. criminal act,
8. to prohibit any advertising of a medical device that is contrary to this Law and to confiscate all advertising material
9. to prohibit work of a legal person 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 law on environmental protection ,
11. to order correction of irregularities and shortcomings,
12. to prohibit activities inconsistent with this Law and the by-laws enacted pursuant to the Law,
13. to order ban or temporary ban of clinical trial of medical device in the trial is not in line with thew Law
14. to order other measures for which he/she is authorized by this Law and the by-laws enacted pursuant to the Law.

VI PENALTY/OFFENCE PROVISIONS

Article 154

A legal entity shall be fined by paying EUR 2500 to 5000 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 in the sense 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. fails to report to the Agency, all the relevant changes in the clinical trail (article 60 paragraph 1);
8. 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);
9. produces medicinal products without having manufacturing authorization (article 65 paragraph 1, 2 and 4);
10. produces medicinal products without fulfilling the conditions of article 68 of this Law;
11. fails to enable regular inspection supervision, as well as supervision on Agency's request (article 71 paragraph 1);
12. 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);
13. 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);

14. **The wholesalers are obligated to supply, sale or distribute without compensation only medicinal products with marketing authorization or medicinal products with import authorization or medicinal products for approved clinical trials, as well as medicinal products for further manufacturing.??? Article 73,,4**
15. performs wholesale distribution of medicinal products without possessing wholesale authorization for medicinal products (article 73 paragraph 2)
16. 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);
17. fails to inform the Agency for any change regarding the conditions stipulated in article 74 of this Law (article 77 paragraph 1);
18. imports medicinal product without import authorization in cases stipulated in article 79 paragraph 2 of this Law;
19. performs retailing of medicinal products without fulfilling of the conditions stipulated in article 82 of this Law;
20. 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;
21. 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 occurred in the Republic of Macedonia or in other countries (article 89 paragraph 1);
22. offers direct or indirect financial benefit to the persons who prescribe or administer the medicinal products (article 93 paragraph 1);
23. advertises prescription only medicinal products to the general public through the mass media (article 95 paragraph 1);
24. advertises medicinal product in a manner contrary to article 95 paragraph 3 of this Law misleading the user of the medicinal product;
25. publicly advertises medicinal products through addressing children (article 95 paragraph 4);
26. publicly distributes free samples of medicinal products (article 95 paragraph 5)

27. publicly advertises medicinal products without marketing authorization (article 95 paragraph 6);
28. 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 manipulation (article 104 paragraph 1);
29. 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)
30. fails to withdraw from the market the medicinal product stipulated in article 104 paragraph 2 of the 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);
31. 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 sticker that the medicinal products if of humanitarian origin and free of charge (article 105 paragraph 2);
32. sales medicinal products at price which has not been formed according to this Law (article 109 paragraph 2);
33. markets medical device which is not in accordance with the conditions stipulated in article 116 of this Law;
34. fails to mark its marketed products with the prescribed conformity mark, based on the conformity certificate (article 119 paragraph 1);
35. marks medical device with the CE mark and such marking is not in accordance with this Law (article 119 paragraph 5);
36. 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;
37. 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);
38. wholesales medical devices without being registered in the Register of legal entities for wholesale of medical devices (article 126 paragraph 2);
39. buys and sells medical devices contrary to the article 126 paragraph 3 and 4 of this Law;

40. wholesales medical devices without fulfilling the conditions stipulated in article 127 of this Law;

41. markets medical device which is marked and/or contains instructions for use contrary to article 132 of this Law;

42. performs clinical trails of medical devices without fulfilling the conditions and principles of good practices stipulated in article 133 paragraph 2 of this Law;

43. implements procedure for clinical trails of medical devices contrary to article 133 paragraph 3 of this Law;

44. commences with clinical trials of medical device without reporting it to the Agency (article 134 paragraph 1);

45. fails to inform the Agency about all relevant changes of clinical trials (article 135 paragraph 1);

46. 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);

47. 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 1000 to 2000 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 600 to 1000 in MKD equivalent.

Article 155

A legal entity shall be fined by paying EUR 1500 to 3000 in MKD equivalent for misdemeanor if:

1. fails to inform the Agency not later than six 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 35)

2. fails to regularly inform the Agency about every smaller changes of type IA and type IB in the procedure for marketing (article 38);
3. performs analytical, pharmaco-toxicological and clinical trials contrary to article 50 of this Law;
4. performs paharmaco-toxicological i.e. preclinical trials of the medicinal product contrary to the principles of good laboratory practice (article 52 paragraph 1);

5. performs clinical trials of medicinal products without submitted results from analytical and pharmacological and toxicological investigation or test of medicinal product which influences the genetic code of the human (article 54 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);

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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 updated reports on the safety of the medicinal product, every six months, in the 2 year period for any new obtained marketing authorization and annually 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 issues results 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 800 to 1500 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 600 to 1000 in MKD equivalent.

MEASURES OF BANNING OF PERFORMING ACTIVITY OR PROFESSION SHOULD BE IDENTIFIED WITH STANISLAVA FOR THE ARTICLES 146 AND 147.

Article 156

Healthcare professional shall be fined in amount of EUR 600 to 1000 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).

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VII TRANSITIONAL AND FINAL PROVISIONS

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1. Establishing the Agency
2. Appointing the director and Management Board
3. Issuing the Statute of the Agency
4. Issuing by-laws
5. Harmonisation timeframe:
    - data exclusivity for generics (proposal: 2+2+2+2+2)
    - data exclusivity for new indication for well established use
    - data exclusivity for additional new indication/significant data
    - data exclusivity for switch Rp-OTC
    - CTD format of documentation
    - harmonisation of requirements for legal/natural persons
    - harmonisation of documentation for already authorised prod.
    - Braille labelling
    - Databases and registers