From the Ministry of Health:

Regulation on the Registration of Medicinal Products for Human Use

SECTION ONE

Objective, Scope, Legal Basis and Definitions

Objective

Article 1- The objective of this Regulation is to set forth the norms and principles and the implementations pertaining to registered medicinal products for human use, for the purpose of achieving the desired efficiency and reliability as well as the required quality in medicinal products for human use.

Scope

Article 2- This Regulation shall comprise medicinal products for human use which are manufactured industrially or imported and the real and legal persons who have applied for the registration and/or have been granted the registration of such products.

However, this Regulation shall not apply to;

a) Any product prepared in a pharmacy specifically for a patient in accordance with a prescription and commonly referred as the magistral formula,

b) Any product prepared in a pharmacy in accordance with the formulas of a pharmacopoeia, intended to be supplied directly to patients served by the pharmacy in concern and commonly referred as the officinal formula,

c) Medicinal products intended to be used in research and development studies, without prejudice to the provisions of the Regulation on Clinical Trials, published on the Official Gazette dated 29/01/1993, with no. 21480,

d) Any semifinished products intended for further processing by an authorised manufacturer,

e) Any radionuclides in the form of sealed sources,

f) Whole blood, plasma or blood cells of human origin.

Legal Basis

Article 3- Based on the Law no. 1262, dated 14/05/1928, on Pharmaceutical and Medicinal Preparations, article 3/k of the Fundamental Healthcare Law dated 07/05/1987, with no. 3359, article 8 of the Law dated 23/06/1983, with no. 2857 on Blood and Blood Products and article 43 of the Decree Law no.181 on the Organisation and Duties of the Ministry of Health;

This Regulation has been prepared in line with the directive no. 2001/83/EC on medicinal products for human use, for the purpose of harmonising with the relevant legislation of the European Union pertaining to medicinal products for human use.

Definitions

Article 4- For the purposes of this Regulation, these terms shall bear the following meanings;

a) Ministry: The Ministry of Health,

b) Law: The Law no. 1262 on Pharmaceutical and Medicinal Preparations,

c) Medicinal Product for Human Use/Product: Any natural and/or synthetic origin active substance or combination of substances administered to human beings with a view to treating and/or preventing a disease, making a diagnosis, correcting or modifying a physiological function,

d) Registered Medicinal Product for Human Use: A medicinal product for human use, approved by the Ministry, presented into the market in ready form, in a special package, with a specific name,

e) Substance: Any matter the origin of which may be human (human blood and human blood products), animal (micro-organisms, whole animals, parts of organs, animal secretions, toxins, extracts, blood products), vegetable (micro-organisms, plants, parts of plants, vegetable secretions, extracts), chemical (elements, naturally occurring chemical materials and chemical products obtained by chemical change or synthesis),

f) Immunological Product:Any agent used to produce active immunity, such as cholera vaccines, BCG, polio vaccines, smallpox vaccines; any agent used to diagnose the immunity status, such as tuberculin and tuberculin PPD, brucellin, Schick ve Dick tests; any agent containing vaccines, toxins and serums used for producing passive immunity, such as diphteria antitoxin, anti-smallpox globulin, antilymphocytic globulin; any medicinal product comprising allergen products intended to alter or define a specific immunological response acquired against an allergen agent,

g) Radiopharmaceutical: Any product prepared for medical purposes, which contains one or more radionuclides within its structure, when ready for use,

h) Radyonuclide: Radioactive characterised atom emitting one or more ionising radiation upon self-disruption of the nucleus,

i) Radioactive Substance: Any substance containing radionuclides in the form of composition, mixture and compound, the nuclei of which are self-disrupted upon the emittance of one or more ionising radiation,

j) Radyonuclide Generator: Any system incorporating a fixed parent radionuclide from which is produced a daughter radionuclide which is to be obtained by elution or by any other method and used in a radiopharmaceutical,

k) Radyonuclide Kit: Any preparation to be reconstituted or combined with radionuclides in the final radiopharmaceutical, usually prior to its administration,

l) Radyonuclide Precursor: Any other radionuclide produced for the radiolabelling of another substance prior to administration,

m) Blood Product: Medicinal products based on blood constituents which are prepared industrially by public or private establishments, such as medicinal products including, in particular, albumin, immunoglobulins and coagulating factors,

n) Active Substance: Pharmacological active substances used in medicinal products for human use,

o) Excipients: Substances, except for the active substance(s), included into the composition of a product,

p) Starting Agents: Any substance used in the manufacture of a product, except for packaging materials,

q) Finished Product: Any product which has surpassed all manufacturing phases and is ready for use in its final package,

r) Registration transactions: Inspection and approval transactions conducted by the Ministry for the market placement of a product,

s) Registration: Document drafted by the Ministry, indicating that the product has been manufactured in accordance with a specific formula, a given pharmaceutical form and dosage, in line with acceptable product information and showing that the product may be introduced into the market,

t) Plasma: Liquid part where the blood separates from its cells and which only contains blood proteins,

u) Batch: The amount obtained in a single production cycle during the manufacture of a product, providing homogeneity,

v) TAEK : Turkish Atomic Energy Authority

w) Specific Activity: Density of activity in a unit mass of a radioactive substance, defined as Curie or Becquerel,

x) Customs Union Area: Customs Union Area defined in paragraph 3 of article 3 of the Association Council Decision No. 1/95 establishing the Customs Union between Turkey and the European Union,

y) Original Medicinal Product: Any product registered/permitted to be introduced into the market for the first time in the world, upon proof of holding scientifically acceptable efficiency, quality and safety in terms of active substance(s),

z) Generic Medicinal Product: Any medicinal product holding the same qualitative and quantitative composition with the original product in terms of the active substances and the bioequivalence of which has been proven with adequate bioavailability studies.

SECTION TWO

Application for Registration

Registration

Article 5- No medicinal product may be placed on the market unless a registration has been issued by the Ministry in accordance with the provisions of this Regulation.

Registration transactions shall also be required for radionuclide generators, radionuclide kits, radinuclide precursors, radiopharmaceuticals and industrially prepared radiopharmaceuticals.

A marketing authorisation shall not be required for a radiopharmaceutical prepared at the time of use by a person or by an establishment authorised, according to national legislation, to use such medicinal products in an approved healthcare establishment exclusively for authorised radionuclide generators, kits or radionuclide precursors in accordance with the manufacturer's instructions.

Application

Article 6- Any real or third person resident within the boundaries of Turkey, shall prepare and present to the Ministry, all particulars and documents required for obtaining a registration for market introduction of a product and to be submitted at the registration application specified in Annex-I of this Regulation, in accordance with the format envisaged in the referred Regulation for each pharmaceutical form.

Persons Eligible to Apply for Registration

Article 7 – In accordance with article 5 of the relevant Law, the following requirements shall be fulfilled by applicants, in order to place a product into the market;

a) Real persons should have graduated from a school providing education in the branches of pharmacy, medicine or chemical sciences and should avail of the authority to practice their profession in Turkey,

b) Legal persons should employ someone with the title of an "authorised person", carrying the qualities specified in item (a) and availing of the accumulation of information and experience with regard to the product(s) for which an application is submitted.

Real persons who are dentists and hold the right to practice their profession in Turkey, shall avail of the right to apply for registration with regard to products used in dental practice.

Particulars and Documents to be Submitted at the Application

Article 8- Real and legal persons intending to obtain a registration for a product, shall apply to the Ministry with the particulars prepared in accordance with Annex-I of this Regulation and documents proving that the following have been conducted;

a) Notary-public certified copy of the diploma indicating that the applicant may practice one of the professions specified in article 7 of this Regulation,

b) Certified document indicating that the applicant is authorised to submit an application,

c) In the event of the applicant being a legal person, the original version or a copy of the commercial registry gazette indicating the objectives for the establishment of the company, the relevant partners, duties and titles of the persons responsible,

d) Name or corporate name, permanent address, e-mail address, telephone and fax numbers of the applicant,

e) Name, permanent address, telephone and fax number of the manufacturer,

f) Name of the product,

g) Quantitative and qualitative particulars of all the constituents of the product in daily terminology except for the empirical chemical formula, its international non-proprietary name (INN) recommended by the World Health Organisation, where applicable,

h) Description of the manufacturing method,

i) Therapeutic indications, contraindications and adverse reactions,

j) Dosage, pharmaceutical form, method and route of administration, shelf life and amount in package,

k) Indication of the disposal method of waste products, upon taking into consideration the storage conditions of the product, its administration to patients, and the potential risks presented by the medicinal product for the environment,

l) Description of control methods used by the manufacturer (quantitative and qualitative analyses of constituents and finished products, sterility tests, pyrogen substances, tests for measuring the presence of heavy metals, stability tests, biological and toxicity tests, controls conducted during the intermediate phase of manufacture),

m) Results of physico-chemical or microbiological tests,

n) Toxicological and pharmacological tests and clinical trials,

o) In case of import products/licensed manufacture, summary of product characteristics (SPC) drafted by the company of origin and indicating the term of validity, package leaflet and mock-ups of the package,

p) In case of import products, the document drafted by the company of origin and the Turkish translation of the document in question, indicating that the real or legal person conducting the importation is the sole authorised representative for the importation, registration and sale of the product in question, or the co-marketing authority, where applicable,

q) In case of licensed manufacture of the product, the document drafted by the company of origin and the Turkish translation of the document in question, indicating that the real or legal person conducting the manufacture is the sole authorised representative for the manufacture, registration and sale of the product in question, or the co-marketing authority, where applicable,

r) GMP document approved by the Ministry or the competent authority of the relevant country, indicating that the manufacturer may manufacture in accordance with Good Manufacturing Practice rules,

s) In the event that the applicant is not the manufacturer, notary-public certified toll manufacturing agreement concluded with a manufacturer availing of the conditions specified in the Regulation on Manufacturing Sites of Medicinal Products for Human Use, published on the Official Gazette dated 23/10/2003, with no. 25268,

t) With regard to the product for which an application is submitted, the list of other countries where an application has been submitted and the certified Pharmaceutical Product Certificate issued by the competent authority in the other country or countries where the product has been introduced into the market,

u) Description of the potential risks to be imposed on the environment by the applicable medicinal product upon consideration of the provisions of the Regulation on Radiation Safety, enforced by the Decision dated 24/07/1985, with no. 85/9727 of the Council of Ministers, the Regulation on the Safe Transportation of Radiactive Substances, published on the Official Gazette dated 10/09/1997, with no. 23106 , the Regulation on Radiation Safety published on the Offical Gazette dated 24/03/2000, with no. 23999 and the Regulation on the Wastes Formed in the Use of Radioactive Substances, published on the Official Gazette dated 02/09/2004, with no. 25571,

v) In addition to the abovementioned requirements, a registration application for marketing a radionuclide generator shall also require the submission of detailed description of the system or the constituents forming the system due to the potential impact on the quality and composition of the nuclide preparation to be eluated and the qualitative and quantitative particulars of the eluate or sublimate,

w) Summary of product characteristics specified in the legislation pertaining to packaging and labelling and the package leaflet prepared accordingly, the mock-ups of the immediate-outer packaging with the size and design to be presented into the market, the original summary of product characteristics approved by the competent authorities of the other countries in import products/products manufactured under license, package leaflet and package mock-ups,

x) In the event that the product for which a registration application is submitted, has been rejected, recalled or suspended by the competent authority in other countries or has been withdrawn by the applicant, the list of these countries, the registered name of the country in question, the date of the transactions conducted and the relevant justification of such transaction.

Any update of the information specified in this article shall be communicated to the Ministry.

Abbridged Application

Article 9- Without prejudice to the provisions of the Decree Law dated 24/06/1995,with no. 551, on the Protection of Patent Rights;

a) In abbridged applications, the applicant shall not be required to present the results of toxicological and pharmacological tests and clinical trials, provided that one of the following points is proved:

1) The medicinal product shall be mostly similar to a medicinal product which previously registered in Turkey and the marketing registration holder of the original medicinal product shall have consented to the use of

the toxicological, pharmacological and/or clinical references contained in the dossier of the original medicinal product for the purpose of evaluating the referred application,

2) Any constituent(s) of the medicinal product shall have a well-established medical use, determined by means of detailed scientific bibliography and with a reasonable efficiency and acceptable level of reliability,

3) The medicinal product shall be essentially similar with a medicinal product which has been registered in accordance with the current legislative provisions and has completed its data exclusivity period. The data exclusivity period called for by this subparagraph, shall apply on the original products for which no generic registration application has been submitted in Turkey until 01/01/2005, among the original products registered for the first time after 01/01/2001 in one of the countries within the Customs Union Area and the original products to be registered for the time after 01/01/2005 in one of the countries of the Customs Union Area and shall be 6 (six) years to begin as of the first registration date in the Customs Union Area and to be limited with the patent period of the relevant molecule in Turkey.

However, in the event of a different therapeutical indication, route of administration, dosage being envisaged from those of the medicinal products which have been introduced into the market, it shall be necessary to submit the results of the relevant clinical trials and where necessary the results of toxicological, pharmacological studies.

b) With regard to new medicinal products containing recognised constituents, but which have not yet been used in combination for therapeutical purposes, it shall be necessary to present the results of the relevant toxicological and pharmacological tests and clinical trials. However, it shall not be obligatory to present the references pertaining to each constituent.

In compliance with subparagraph (2) in item (a) of the first paragraph of this article, in the event of the presentation of bibliographical references based on published data, the applications shall be submitted in accordance with Annex I.

In exceptional cases constituting a severe threat for public health, the Ministry may take into consideration the registration applications of generic products, which have been presented upon taking as basis the data pertaining to the toxicological, pharmacological and clinical data published on literature, independent from the provisions set forth in this article.

Registration in Special Cases

Article 10- In belowmentioned special cases, registration may be issued within the framework of the decision of the Ministry, provided that more advanced studies are conducted in consequence pursuant to the issuance of registration and the communication of the adverse effects pertaining to the medicinal product:

a) The therapeutical indications pertaining to the relevant product are not sufficient to enable the applicant to provide detailed evidence,

b) Detailed information may not be provided in the light of the current scientific data,

c) The collection of such data results to be in violation of the accepted ethical norms.

In the event of being registered under special conditions, the package and the patient leaflet of the relevant product shall contain statements indicating the current status of the product and that the product results to be still insufficient in terms of certain aspects.

Summary of Product Characteristics

Article 11 – Summary of Product Characteristics shall contain;

a) Name of medicinal product,

b) Quantitative and qualitative composition in terms of the active substances and constituents of the excipient, knowledge of which is essential for proper administration of the medicinal product, the usual common name or chemical description,

c) Pharmaceutical form,

d) Pharmacological properties and pharmacokinetic properties to an extent that may be beneficial within the scope of the therapeutical purpose,

e) Clinical particulars;

1) Therapeutic indications,

2) Contra-indications,

3) Adverse effects indicating the incidence and severity

4) Special precautions for use; in the case of immunological medicinal products, any special precautions to be taken by persons handling such products and administering them to patients, together with any precautions to be taken by the patient,

5) Use during pregnancy and lactation,

6) Interaction with other drugs and other forms of interactions,

7) Posology and method of administration for adults and where necessary for children

8) In the case of overdose, symptoms, emergency procedures and antidotes,

9) Special warnings,

10) Effects of ability to drive and use machines,

f) Pharmaceutical properties;

1) Major incompabilities,

2) Shelf life, when necessary after reconstitution of the medicinal product or when the immediate packaging is opened for the first time,

3) Special precautions for storage,

4) Nature and contents of immediate package,

5) Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product, if appropriate,

g) Name, address, telephone and fax numbers of the registration holder,

h) With regard to radiopharmaceuticals, full details of internal radiation dosimetry,

i) With regard to radiopharmaceuticals, additional detailed instructions, information on preparations and quality control of such preparation and, where appropriate, maximum storage time during which any intermediate preparation such as an eluate or the pharmaceutical which is ready for use will conform with its specifications,

Expert Reports

Article 12- When submitting an application, the registration holder shall submit expert reports signed by relevant experts for each chemical, pharmacological, biological, toxicological and clinical section.

The duties of the experts who will prepare the reports shall be as follows in accordance with their qualities:

a) To perform their duties within their own discipline (analysis, pharmacology and similar experimental sciences, clinical trials) and to provide an objective description of the qualitative and quantitative results,

b) To define their observations according to Annex-I and specify the following aspects, in particular;

1) With regard to analysis experts, to determine with the control methods used by the manufacturer, whether the medicinal product is in compliance with the declared composition,

2) To observe the toxicity and pharmacological properties of the medicinal product,

3) In case of clinicians, to specify whether the particulars and documents presented to the Ministry by the applicant in accordance with the provisions of this Regulation, are accurate with regard to the impact on the patients being treated with the product in question, whether the product is well tolerated by the patient and the recommendations of the clinician with regard to posology, contraindications and adverse effects.

The curriculum vitae of the expert, the declaration of his/her professional relation with the applicant and the justification of the particulars and documents used for bibliographical application should be specified where necessary.

Detailed reports of the experts, shall constitute a part of the particulars and documents attached to the application submitted by the applicant to the Ministry.

SECTION THREE

Evaluation of the Application for Registration and Issuance of Registration

Preliminary Analysis

Article 13- The Ministry shall conduct a preliminary analysis in order to evaluate whether the application dossier presented to the Ministry for the purpose of obtaining registration for medicinal product for human use is complete and full in terms of the information and documents required to be submitted in accordance with the nature of the application. Relevant evaluation shall be conducted within 30 (thirty) days as of the receipt of the application dossier by the Ministry and the result will be communicated to the applicant. In case of deficiencies in the application dossier, the applicant shall complete these within 30 (thirty) days. The second preliminary analysis to be conducted upon the remedy of the deficiencies and submittal to the Ministry, shall be finalised within 30 (thirty) days.

Return of application

Article 14- In case of detection of the following conditions in the preliminary analysis conducted by the Ministry, within the scope of article 13 of this Regulation, the application shall be rejected according to the procedures and returned to the applicant:

a) When the applicant does not carry the qualities specified in the relevant Law and article 7 of this Regulation,

b) When the application is subject to a second preliminary analysis with its deficiencies not being remedied.

Period of Registration

Article 15- The Ministry shall analyse the registration application which has undergone a preliminary analysis and results to be complete, for checking whether the registration conditions have been fulfilled and shall finalise the process within 210 (two hundred and ten) days after the acceptance of the application. However, the period required for the fulfillment of the conditions demanded by the Ministry from the applicant, shall not comprise extraordinary cases and the evaluations of the institutions other than the Ministry.

Furthermore, the 210-day period shall be halted in the following cases:

a) In order to verify the accuracy of the particulars and documents used in the manufacture of the product and presented with the application in accordance with item (m) of the first paragraph of article 8 of this Regulation, until the remedy of the deficiencies in cases where request is made by the Ministry for the presentation of the starting materials and if necessary the intermediate products and the other constituent substances to be tested in a national laboratory or a laboratory accredited by the Ministry for the abovementioned purpose,

b) Until the presentation of the relevant particulars and documents when request is made by the Ministry to the applicant during the registration process for additional particulars and documents within the scope of article 8,9,10 and 11 of this Regulation,

c) Until relevant written or oral explanation is provided when request is made by the Ministry for the provision of oral or written explanation from the applicant.

Registration Criteria

Article 16- The Ministry shall take into consideration the following criteria, when issuing registration:

a) Have proven efficiency in the envisaged conditions of use,

b) Have proven reliability,

c) Contribute to the current treatments,

d) Have the adequate technical and pharmaceutical properties.

Evaluation of Applications

Article 17- The following aspects shall be taken into consideration while evaluating the applications:

a) The information and documents proving the efficiency, reliability and quality of a product shall be analysed from a scientific and technological aspects,

b) The product shall be tested in a national laboratory or a laboratory accredited by the Ministry for this purpose, in order to determine the accuracy of the product formulation and the applicability of the methods used by the manufacturer in the control of the product,

c) The control tests conducted for determining the viral contamination in blood products shall prove the reliability of the product and the source of the plasma used in the preparation of this product shall be specified,

d) In the event of substances of animal origin in the formulations of radiopharmaceuticals/kits, a document provided by the official authority indicating the absence of BSE virus shall be provided; in the presence of blood and plasma products, tests for viral contamination, AIDS, hepatitis and similar tests shall be requested.

Refusal of the Request for Registration

Article 18- During the evaluation process of the application submitted to the Ministry, the application shall be rejected in the detection of the following;

a) The potential risk is higher than the effect of the treatment under normal conditions of use,

b) Therapeutical effect is insufficient or is not sufficiently proven,

c) Bioavailability is not sufficient in products regarded as relevant,

d) No contribution is provided to current treatments,

e) The qualitative and quantitative formula is not consistent with the formula submitted at the application or no result is obtained when the communicated control methods are implemented; there is persistent inconsistency in the controls conducted for the second time, despite the warnings made to the applicant with regard to the limits beyond acceptable limits of the declared specifications.

Notification and Objection

Article 19 – In case of refusal of the registration application, this decision shall be communicated to the applicant with the relevant justification. The applicant shall hold the right to submit a written objection to the decision within 30 (thirty) days. In the event no objection is submitted within 30 (thirty) days, the application documents shall be returned to the applicant.

The objection submitted shall be evaluated by the Ministry within 90 (ninety) days and the result will be communicated to the applicant. During the evaluation of the objection, the applicant will be granted the right for oral explanation and defense, where necessary. The decision to result from the evaluation of the objection shall be final and no objection may be submitted to this decision.

Issuance of Registration

Article 20- As a result of the inspection and evaluation of the information and documents submitted by the applicant to the Ministry, the product determined to be in compliance with the aspects envisaged by this Regulation shall be drafted and the applicant shall be duly informed.

A second local or import registration shall not be issued for any product with the same formulation and pharmaceutical form, registered by the Ministry, to the same real or legal person, even if the product has a different commercial name.

The names of products for which a registration is issued by the Ministry, shall be declared on the Official Gazette with the name and surname as well as the registration number of the application holder.

Validity of Registration

Article 21- Registrations shall be valid for 5 (five) years. The registration holder shall present to the Ministry at least 3 months (three) months before the termination of the validity of the registration, the relevant pharmacovigilance data as well as the particulars pertaining to the quality, reliability and efficiency of the product, comprising any variations that has been conducted as of the registration date.

Suspension of Registration

Article 22 – In the event of the detection of the following in a registered product, the registration pertaining to the product shall be suspended by the Ministry:

a) The emergence of the harmful effects in normal conditions of use,

b) Detection of the lack of or insufficient therapeutical effect ,

c) Production with a formulation other than the formulation taken as basis in the registration,

d) Performing variations not informed to and/or not approved by the Ministry, in the formulation, dosage, pharmaceutical form, package and summary of product characteristics taken as basis in the registration,

e) Failure of the applicant to take into consideration the scientific and technical advancements in terms of the manufacture and control methods and the failure to perform any variation that may be required for the manufacture and control of the medicinal product according to generally accepted scientific methods and to present them to the approval of the Ministry,

f) Failure to take into consideration any warning made with regard to the products determined to be defective as a consequence of the market controls conducted and the continuation of defective manufacture,

g) Failure to comply with the relevant legislative provisions pertaining to the package and labelling and non-consideration of the warning made to the registration holder,

h) No response provided by the registration holder to the instructions and warnings of the Ministry on the product,

i) Detection of errors in the particulars and documents presented for the registration of a product in accordance with the provisions of this Regulation,

j) Failure to actually place a medicinal market into the market 3 (three) years after issuance of registration,

k) Failure to submit a renewal application in accordance with article 21 of this Regulation despite the termination of the validity of the registration,

l) Decision to suspend the registration in consequence to the risk/benefit evaluation conducted by the Ministry with regard to the notifications received within the framework of the pharmacovigilance implementations.

The manufacture of a product the registration of which is suspended, shall be halted. The decision to be taken with regard to the products in distribution and sale shall be taken by the Ministry, upon consideration of the justification for suspending the registration.

Annulment of Registration

Article 23- In the presence of one of the following conditions, the registration issued for the product shall be annulled:

a) The failure to present latest within 6 (six) months, by the registration holder, the particulars and documents proving the contrary of the justification for suspension pertaining to products the registration of which has been suspended due to one or more conditions specified in article 22 of this Regulation,

b) Renouncing to manufacture, upon the demand of the registration holder and where deemed appropriate by the Ministry.

The manufacture of a product the registration of which has been annulled, shall be halted. The decision pertaining to the products in distribution and sale shall be taken by the Ministry, upon consideration of the justification for the revocation of the registration.

The names of products the registrations of which have been annulled by the Ministry, shall be declared on the Official Gazette, with the name, surname of the registration holder and the relevant registration numbers.

Responsibilities of Registration Holders

Article 24- The registration holder shall be responsible for the following topics towards the Ministry with regard to product of which he/she is holding the registration:

a) Manufacturing the product in compliance with the specifications presented in the annex of the application and accepted by the Ministry,

b) Considering the scientific and technical progress in terms of manufacture and control methods and the presentation to the approval of the Ministry any amendment to enable the manufacture and control of the medicinal product with the generally accepted scientific methods,

c) Updating, when necessary, summary of product characteristics and patient leaflet for the purpose of enabling a correct and safe use of the product,

d) In the event of any variation pertaining to the product, communicating the variations to the Ministry within the framework of the pertinent guideline provisions,

e) Providing response to the topics requested by the Ministry, in relation with the product,

f) Fulfilling the obligations within the framework of pharmacovigilance implementations, in consequence to the market introduction of the product,

g) Ensuring the procurement of measures for the purpose of preventing the contamination of infections in case of a biological product,

h) Securing the market availability of the product of which he/she holds the registration,

i) Forthwith communication with all relevant justifications, to the Ministry, of all measures taken for the purpose of suspending the registration of a product or withdrawing it from the market, due to its efficiency or for safeguarding public health,

j) Fulfilling the requirements of the legislation pertaining to the product,

k) Paying specified dues and fees pertaining the products.

Change of Registration Holder

Article 25- The registration holder of a product registered by the Ministry may be changed. The transactions pertaining to the change of the registration holder shall be presented to the Ministry with the following particulars and documents:

a) The decision taken by the relevant court/execution office, pertaining to the change of the registration holder, or the contract drawn up before a notary-public and comprising the following topics,

1) Name, registration date and number of the product undergoing the transaction of change of registration holder,

2) Name and address of real or legal persons that will grant the registration and receive the registration with the change of the registration holder,

3) Minutes indicating that the current complete and updated product dossier which has been approved by the Ministry has been submitted in full to the person to whom the registration is transferred,

b) The person receiving the registration upon the change of the registration holder shall present to the Ministry the following particulars and documents indicating that he/she avails of the capacity to fulfill all responsibilities expected from the registration holder;

1) Notary-public certified diploma copy indicating that he/she is a member of the profession specified in article 7 of this Regulation, for the persons that may apply for registration,

2) In the event of a legal person, the original or the copy of the commercial registry gazette indicating the establishment objectives, partners and responsible persons of the company,

3) Within the framework of pharmacovigilance implementations, the curriculum vitae, address, telephone and fax numbers of the person responsible for product safety, and the document defining the job of this person,

4) The document defining the scientific service within the framework of the Regulation on the Promotional Activities of Medicinal Products for Human Use, published on the Official Gazette dated 23/10/2003, the address, telephone and fax numbers of this service,

c) The name, surname, address, telephone and fax numbers of the person receiving the registration with the change of registration holder, the summary of product characteristics, instructions for use, a sample each from the immediate and outer packages, and in case of transfers conducted via a notary-public, the original registration previously issued for the product in question.

In the event of an import product, application shall be made to the Ministry where, in addition to the abovementioned particulars and documents, the original document indicating the change of the real or legal person authorised for the registration and sale of the relevant product in Turkey and the notary-public certified Turkish translation of the referred document will be submitted.

In the event that the company of origin changes unilaterally the real or legal person authorised for the registration and sale of the product in question in Turkey, the original document bearing the new date and indicating the authority granted by the company of origin for the registration and sale of the product in Turkey, its notary-public certified Turkish translation, and except for the item (a) of the first paragraph of this article, the current complete and updated product dossier approved by the Ministry as well as all requirements necessitated by this article.

With regard to all variations to be performed on the products, a separate application shall be submitted to the Ministry, in accordance with the relevant guideline provisions of the variations. The application submitted

with regard to the variation, shall be evaluated by the Ministry upon the completion of the transactions for the change of the registration holder of the product.

The Ministry shall complete within 60 (sixty) days the application for the change of the registration holder accompanied with complete particulars and documents.

Obtaining Sales Permit

Article 26- Before the first market introduction of the medicinal product of which he/she holds the registration, the registration holder shall present to the Ministry two samples of the final forms to be introduced into the market for the purpose of obtaining a sales permit. The Ministry shall analyse the samples of the product to which it will grant registration, in terms of the accuracy of the information on the patient leaflet, package and label as well as price adequacy. It shall be obligatory to obtain a new sales permit for the transactions leading to the change of the package and label information and/or properties taken as basis in the registration of the product.

In case the product for which a registration is obtained, is a blood product or a medicinal product containing a blood product, the registration holder shall apply to the Ministry for obtaining a sales permit for each batch of the product in addition to the points specified in the first paragraph before introducing the product into the market. Sales permit shall be granted upon the conduct of the analyses on the product from this batch, in a national laboratory or a laboratory appointed by the Ministry for this purpose.

The following particulars and documents shall be submitted to the Ministry for the purpose of obtaining a sales permit for blood products and medicinal products for human use containing a blood product, upon specification of the amount requested to be introduced for sale:

a) Name and content of the product,

b) Batch release certificate issued by a national or international accredited laboratory and approved by the National Health Authority, for each batch,

c) Original analysis certificate approved by the technical manager of the production center for each batch,

d) Original document (certified by apostille) drafted by the company of origin, indicating the country where each batch is registered/manufactured and the countries where each batch is sold,

e) The rules taken as basis in plasma donation, plasma collection date and donor type (volunteer, paid) and the list of donors, where necessary,

f) The document issued by the abovementioned laboratories, indicating that each donor has been tested for Hepatitis B, Hepatitis C and HIV ½, that HCV RNA test has been applied in the plasma pool and reflecting the relevant results,

g) The original document (certified by apostille) to be issued by the manufacturing company, indicating that the donors are safe in terms of any disease or suspect of disease with regard to the Creutzfeld-Jacob (CJ) disease and that there is no diagnosis of CJ disease among the donors, for each batch.

In case of the product for which a registration is obtained, being an immunological product , the registration holder shall apply to the Ministry for obtaining a sales permit for each product batch in addition to the points specified in the first paragraph before introducing the product into the market.

The following particulars and documents shall be presented to the Ministry, upon the communication of the amount requested to be introduced for sale in order to obtain a sales permit for immunological products:

a) Batch/ Lot Release Certificate issued by a national or international accredited laboratory and approved by the National Health Authority, for each batch,

b) Original analysis certificate approved by the technical manager of the production center for each batch.

Variations Pertaining to the Registration

Article 27- All variations pertaining to the product, to be performed in consequence to the issuance of the registration of a product, shall be submitted to the Ministry by the registration holder, in accordance with the provisions of the relevant guideline provisions.

SECTION FOUR

Miscellaneous and Final Provisions

Confidentiality

Article 28- The information presented to the Ministry by the applicant for obtaining the registration of a product, shall be confidential. This confidentiality shall be protected by the Ministry.

Penalty Provisions

Article 29- The Turkish Penal Code dated 01/03/1926, with no. 765 and the other relevant legislative provisions shall be applied on those who fail to comply with the provisions of this Regulation.

Revoked Legislation

Article 30- The Regulation on Radiopharmaceuticals, dated 23/12/1993, with no. 21797, the Regulation on the Registration of Medicinal Pharmaceutical Products, published on the Official Gazette dated 02/03/1995, with no. 22218 and the Regulation on the Registration of Blood Products, published on the Official Gazette dated 20/05/2002, with no. 24760 have been revoked.

Temporary Article 1- The registration/permit applications submitted before the enforcement of this Regulation, shall be evaluated in accordance with the legislative provisions in force on the date such applications are submitted.

With regard to the abbridged applications presented in accordance with article 9 of this Regulation of which all provisions except for article 9 shall be enforced on 30/06/2005, the applications submitted in compliance with the application format indicated in the Regulation in force shall be accepted.

Temporary Article 2- The current guidelines shall continue to be applied as is, until the enforcement of the regulation setting forth the rules and procedures pertaining to the permits of the products similar to medicinal pharmaceutical products, and the rules to be applied on the variation applications in medicinal products for human use which have been registered with this regulation or for which a registration has been applied.

Temporary Article 3- For the conduct of the relevant evaluations with regard to the vaccines, antiserums and allergen containing biological products introduced into the market with import permit, persons holding the import permit shall apply for registration with the documents requested by the Ministry, within 1 (one) year of the enforcement date of this Regulation. The import permits of products for which no registration application is submitted within this period shall not be valid.

Temporary Article 4- For the purpose of conducting the relevant evaluations pertaining to the products registered before the enforcement date of this Regulation, in accordance with the Regulation on Radiopharmaceuticals, published on the Official Gazette dated 23/12/1993, with no. 21797, the persons holding the certificate of registration shall apply for registration with the documents requested by the Ministry, within 1 (one) year of the enforcement date of this Regulation. The certificates of registration pertaining to products for which no registration application is submitted within this period shall not be valid.

Enforcement

Article 31- Article 9 and the second paragraph of Temporary Article 1 of this Regulation shall be enforced as of 01/01/2005, as of the publication date, whereas the other provisions shall be enforced as of 30/06/2005.

Execution

Article 32- The provisions of this Regulation shall be executed by the Minister of Health.

Annexes Available in the Printed Version of the Official Gazette.