REGULATION ON THE MARKETING AUTHORIZATION OF MEDICINAL PRODUCTS FOR HUMAN USE

SECTION ONE
Aim, Scope, Base and Definitions

Objective

Article 1- (1) The objective of this Regulation is to set forth the norms and principles and the implementations pertaining to granting marketing authorization procedures, for the purpose of achieving the desired efficiency and safety as well as the required quality in medicinal products for human use.

Scope

Article 2 – (1) This Regulation shall comprise medicinal products for human use which are manufactured industrially or manufactured by a method that includes an industrial process and the real persons and legal entities who have applied for the marketing authorization and/or have been granted the marketing authorization of such products.

(2) This Regulation shall not apply to the following;

a) Any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient commonly known 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 question and commonly known as the officinal formula,

c) Medicinal products intended to be used for research and development trials, without prejudice to the provisions of the Regulation on Clinical Trials of Medicines and Biological Products published in the Official Gazette dated 13/4/2013 and numbered 28617,

ç) Intermediate products intended for further processing by an authorized manufacturer,

d) Any radionuclides in the form of sealed sources,

e) Whole blood, plasma or blood fractions of human origin, excluding plasma and plasma products prepared by a method involving an industrial process,

f) Traditional herbal medicinal products,

g) Homeopathic medicinal products,

ğ) Foods for special medical purposes,

h) Advanced therapy medicinal products.

(3) In cases of doubt, where, taking into account all its characteristics, a product may fall within the definition of a medicinal product and within the definition of a product covered by other relevant legislation the provisions of this Regulation shall apply.

Legal basis

ARTICLE 3 – (1) This Regulation has been drawn up based on the provisions of Pharmaceutical and Medical Preparations Law No. 1262 dated 14/5/1928, paragraph (k) of the first paragraph of Article 3 of the Health Services Basic Law No. 3359 dated 7/5/1987, Article 6 of the Blood and Blood Products Law dated 11/4/2007 and numbered 5624 and Articles 508 and 796 of the Presidential Decree on the Organization of Ministries and Institutions and Organizations and Other Institutions and Organizations Related, Affiliated to Ministries dated 15/07/2018 and numbered 4.

Definitions

ARTICLE 4 - (1) For the purposes of this Regulation; the following definitions shall apply;

a) Labelling: Information on the immediate or outer packaging,

b) Medicinal product for human use means;

1) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings;

2) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis,

c) The trade name of the medicinal product for human use which 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 the name of the marketing authorisation holder.

ç) Risks related to the use of the medicinal product for human use:

1) Risks relating to the quality, safety and efficacy of the medicinal product for human use as regards patients' health or public health, or

2) Risks that may cause undesirable effects on the environment,

d) Strength of the human medicinal product: The content of the active substances expressed quantitatively per dosage unit, per unit of volume or weight according to the pharmaceutical form.

e) Herbal substance: All mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried, form, but sometimes fresh and certain exudates that have not been subjected to a specific treatment, precisely defined by the plant part used and the botanical name according to the binomial system (genus, species, variety and author);

f) Herbal preparation: Preparations obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation including comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates,

g) Herbal medicinal product: any medicinal product, exclusively containing as active ingredients one or more herbal substance or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations,

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

h) Biosimilar medicinal product: A medicinal product for human use that shows a high level of similarity with an authorised reference biological medicinal product in terms of quality, efficacy and safety,

ı) Herbal drug: Pharmaceutical raw material of natural origin,

i) Generic medicinal product: A medicinal product that has the same qualitative and quantitative composition and the same pharmaceutical form as the reference medicinal product in terms of active substance(s) and whose bioequivalence has been proven by appropriate bioavailability studies (Different salts, esters, ethers, isomers, isomer mixtures of an active substance, its complexes or derivatives are considered the same as the active substance unless their properties differ markedly in terms of safety or efficacy. In such cases, additional information 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 various immediate-release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form. The applicant is not required to submit bioavailability studies if he/she fulfills the relevant criteria as detailed in the guidelines for the generic medicinal product.),

j) Active substance: Any substance or mixture of substances intended to be used in the manufacture of a medicinal product for human use and that, when so used, becomes an active ingredient of that product to correct, improve, change physiological functions or to provide pharmacological, immunological or metabolic effect for medical diagnosis,

k) Pharmacopoeia: Turkish Pharmacopoeia (Adaptation of European Pharmacopoeia), European Pharmacopoeia, American Pharmacopoeia, British Pharmacopoeia and Japanese Pharmacopoeia; in cases where these pharmacopeias are not applicable, the pharmacopeia approved by the Agency,

l) Pharmaceutical form: The presentation form of the medicinal product for human use manufactured in accordance with its intended use,

ü) 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,

n) Hybrid application: The marketing authorization application submitted partly with the data of the reference product and partly with the data obtained from the studies of the new product,

o) Immunological medicinal product for human use means any medicinal product for human use comprising:

1) Agents used to produce active immunity, such as cholera vaccine, BCG, polio vaccines, smallpox vaccine; agents used to diagnose the state of immunity, including in particular tuberculin and tuberculin PPD, toxins for the Schick and Dick Tests, brucellin; agents used to produce passive immunity, such as diphtheria antitoxin, anti-smallpox globulin, antilymphocytic globulin or,

2) Any medicinal mean product within the meaning of "allergen agent" which is intended to identify or induce a specific acquired alteration in the immunological response to an allergizing agent or,

3) Products in the structure of immunoglobulin, which are obtained from the blood of animals (rabbit, horse and similar) and have an effect on the human immune system,

ö) Law: Law on Pharmaceutical and Medical Preparations dated 14/5/1928 and numbered 1262,

p) Blood product: Medicinal products based on blood constitutents which are prepared industrially, such medicinal products including, in particular, albumin, coagulating factors and immunoglobulins of human origin,

r) Summary of product characteristics: Written information of the medicinal product for human use prepared for healthcare professionals,

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

ş) Package leaflet: A leaflet containing information for the user which accompanies the medicinal product,

t) Agency: Turkish Medicines and Medical Devices Agency,

u) Licensor company:

1) The company that authorizes the natural or legal person for the marketing authorization and sale of the imported medicinal product for human use in Turkey, or,

2) The company that authorizes the real or legal person for the manufacture, marketing authorization and sale of the medicinal product for human use manufactured with a license in Turkey,

ü) 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),

v) Co-marketed product: A medicinal product for human use that has the same qualitative and quantitative composition and the same pharmaceutical form as an authorized human medicinal product, manufactured at the same manufacturing site, and is completely identical in all respects other than its trade name,

y) Priority Assessment Committee: Committee established in order to prioritize applications in the Agency's business and operations for human medicinal products of strategic importance, which are the first in treatment or diagnosis, bring innovation, or are needed in

terms of public health in order to ensure the sustainability of access to the medicine or the rapid delivery of the medicine to the society; whose working procedures and principles are determined in accordance with the relevant guideline,

z) Radiopharmaceutical: Any medicinal product which, when ready for use, contains one or more radionuclides included for a medicinal purpose,

aa) Radionuclide: A radioactive atom whose nucleus undergoes self-decay and emits one or more ionizing radiation,

bb) Radionuclide 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,

cc) Radionuclide Precursor: Any other radionuclide produced for the radio-labelling of another substance prior to administration,

çç) Reference medicinal product: Any medicinal product for human use authorised or permitted to be introduced on 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),

dd) Marketing authorization: The certificate issued by the Agency showing that a medicinal product for human use shall be manufactured and placed on the market in accordance with the approved product characteristics within the specified formulation and pharmaceutical form and strength,

ee) Marketing authorization holder: The natural or legal person holding the marketing authorization of the medicinal product for human use,

ff) Granting Marketing Authorization: The examination and approval procedure carried out by the Agency in order to place a medicinal product for human use on the market,

gg) Authorized Medicinal Product for Human Use: A medicinal product for human use, approved by the Agency, to be placed on the market in ready for use form, in a special package, with a specific name,

ğğ) Batch (Lot): The amount of a medicinal product for human use obtained in a single production cycle, providing homogeneity,

hh) International and non-proprietary name (International Nonproprietary Name, INN): International name of an active substance accepted or recommended by the World Health Organization, which cannot be subject to property and which should not be used in trademark registration in accordance with the rules of the World Health Organization,

ii) Manufacturing Site: The place where the pharmaceutical form (bulk product) of the medicinal product for human use is manufactured before the immediate packaging, except cases where the medicinal products for human use manufactured with technologies that are not available in our country or are rare, are evaluated by the Agency on the basis of application,

ii) Benefit/risk balance: Evaluation of the therapeutic effects of a medicine together with all the quality, safety and efficacy risks it poses in terms of patients' health or public health,

jj) Excipient: Substances, except for the active substance(s), included into the composition of a medicinal product for human use,

kk) The international non-proprietary name recommended by the World Health Organization, or, if one does not exist, the usual common name.

SECTION TWO
Marketing Authorization Application

Marketing authorization obligation

Article 5 – (1) No medicinal product for human use can be placed on the market a marketing authorisation has been issued by the Agency pursuant to this Regulation.

(2)The authorization shall equally apply to radionuclide generators, kits, radionuclide precursor radiopharmaceuticals and industrially prepared radiopharmaceuticals.

(3) A marketing authorization shall not be required for radiopharmaceuticals prepared at the time of use by a competent person or by an establishment authorized, to use such medicinal products in an approved health care establishment exclusively from authorized radionuclide generators, kits or radionuclide precursors and positron emitting radionuclides in accordance with the manufacturer's instructions.

(4) A marketing authorization shall not be required for unauthorised magistral radiopharmaceuticals in Turkey, if approved by the Agency and provided that the literature showing its efficacy and safety has been proven in the world or in Turkey and has been routinely used is submitted to the Agency. The use of such magistral radiopharmaceuticals shall be limited to the relevant health institution.

(5) In the event that a marketing authorisation application is submitted for the industrial production of these products by persons other than the current permit holders for magistral radiopharmaceuticals that were previously permitted, the permits granted before the date of issuance of the marketing authorisation shall be continue to be valid, provided that they comply with the relevant guidelines. However, if there is a supply problem in the market despite the authorised radiopharmaceutical product being placed on the market, a permit may be requested for a period of up to twelve months, provided that the use of magistral radiopharmaceuticals approved by the Agency is limited in the relevant health institution without seeking a marketing authorisation.

(6) The permission granted by the Agency for magistral radiopharmaceutical medicinal products within the scope of this article shall be valid during the period that the existing personnel qualifications and infrastructure declared as of the application date are preserved.

Marketing authorisation application and application method

ARTICLE 6 – (1) In order to obtain an authorization to place a medicinal product on the market, real or legal persons residing in Turkey shall make an application to the Agency in accordance with Annex-1.

(2) In case of an application, the Agency may give scientific advice to the applicant before the marketing authorisation application or during the granting marketing authorisation process, subject to a fee included in the price list.

(3) Before a marketing authorisation application is made for a medicinal product for human use that does not have an authorised generic and is not subject to a prescription, approval is obtained from the Agency that the medicinal product for human use is not subject to a prescription.

(4) Except for cases deemed necessary by the Agency, force majeure or obligatory cases; marketing authorisation applications shall only be accepted electronically and all correspondence during the marketing authorisation process shall be carried out electronically only.

Persons eligible to apply for marketing authorization

ARTICLE 7 – (1) Pursuant to Article 5 of the Law, those wishing to obtain a marketing authorisation to place a medicinal product for human use on the market shall bear the following conditions;

a) Real persons; having graduated from one of the higher education institutions providing education in the fields of pharmacy, medicine or chemistry and having the authority to practice their profession in Turkey,

b) Legal persons; employing a person who has the qualifications specified in subparagraph (a) of the first paragraph, as an "authorized person",

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

Particulars and documents to be submitted at the application

ARTICLE 8 – (1) Real persons or legal entities intending to obtain a marketing authorization for a product, shall apply to the Agency with the particulars prepared in accordance with Annex-I of this Regulation and documents proving that the following have been conducted;

a) Diploma or its notarised copy showing that applicant may practice one of the professions specified in article 7 of this Regulation, or a graduation certificate from the Higher Education Council.

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

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

ç) Name or corporate name, permanent address, registered e-mail (KEP) address, telephone and fax number of the applicant.

d) Name, permanent address, telephone number and fax number of the manufacturing site(s) for all manufacturing steps.

e) Name of the medicinal product for human use.

f) The qualitative and quantitative expression of all active substance(s) and excipients in the content of the medicinal product for human use, using common names of the active substance(s).

g) Description of the manufacturing method,

ğ) Therapeutic indications, contra-indications and adverse reactions.

h) Posology, pharmaceutical form, method and route of administration, shelf life, package size.

ı) Any precautionary and safety measures to be taken for the storage of the medicinal product, its administration to patients and for the disposal of waste products in accordance with the provisions of the Waste Management Regulation published in the Official Gazette dated 2/4/2015 and numbered 29314 together with an indication of potential risks presented by the medicinal product for the environment.

i) Description of the control methods employed by the manufacturer and presented in accordance with the pharmacopoeia when applicable (Where deemed appropriate by the Agency, some of these analyses, tests and controls, specified on product basis, may be omitted, provided doing so does not affect security, safety and quality).

j) Results of pharmaceutical tests consisting of physicochemical, biological or microbiological tests.

k) Results of preclinical tests consisting of toxicological and pharmacological tests.

l) Results of clinical trials.

m) In case clinical trials are conducted outside of Turkey, the applicant's statement that it meets the ethical requirements set forth in the Regulation on Clinical Trials of Medicines and Biological Products.

n) In the case of an imported product, a document showing that the importing real person or legal entity is the sole representative authorized for importing, marketing authorization and selling the product in Turkey, and in the case of co-marketing, a document issued by the licensor showing that a real person or legal person other than the sole authorized representative in Turkey is also granted co-marketing authorization.

o) In the case of a product manufactured on license, a document issued by the licensor showing that the real person or legal entity manufacturing the product is the sole authorized representative that can manufacture and sell the product in Turkey, and in the case of co-marketing, a document issued by the licensor showing that a real person or legal person other than the sole authorized representative in Turkey is also granted co-marketing authorization.

ö) In the case of co-marketing of a product manufactured or to be manufactured in Turkey, on co-marketing the written consents of the real or legal person who will carry out on co-marketing.

p) In applications for co-marketed human medicinal products, commitment stating that the medicinal products for human use subject to co-marketing are exactly the same, all variation applications will be made simultaneously and in case there is more than one manufacturing site of the product subject to co-marketing, all of the medicinal products for human use subject to co-marketing will be manufactured only in one of these manufacturing sites.

r) For applicants who do not have a Nuclear Regulatory Authority license, in case it is desired to authorize a company licensed by the Nuclear Regulatory Authority for the distribution and sale of locally manufactured radiopharmaceutical products, and for import, distribution and sale of imported radiopharmaceutical products; Agreement between two companies, where the Nuclear Regulatory Authority-licensed company is the sole authority for the said transactions, and the registration certificate of the parties.

s) In addition to the written declaration submitted in line with the second paragraph of Article 14 of the Regulation on the Manufacturing Plants of Medicinal Products for Human Use published in the Official Gazette dated 21/10/2017 and numbered 30217 regarding the manufacturing sites of the active substance for human medicinal products; document issued by the Agency showing that the manufacturing is made in accordance with the good manufacturing practices guidelines belonging to the active substance manufacturing site(s) of the products other than the products that are deemed appropriate to be submitted after the marketing authorization application in the assessment made by the Priority Assessment Committee for the for the active substance(s) included in the scope of audit by the Agency; document issued by a competent health authority accepted by the Agency showing that the manufacturing is made in accordance with the internationally accepted good manufacturing practices guidelines for the manufacturing steps of substances for which no document is issued by the Agency or Manufacturing Site Authorization for active substance manufacturing site(s) operating in Turkey; for manufacturing site(s) of active substance not included in the scope of audit by the Agency, where applicable, for the intermediate product used in manufacturing process of the active substance the following documents shall be required:

1) A document issued by an authorized health authority to these places, showing that the active substance(s) are manufactured in accordance with internationally accepted good manufacturing practices. In cases where this document is not physically issued, the information or document accepted by the Agency showing that the active substance/s are manufactured in accordance with internationally accepted good manufacturing practices.

2) In cases where it is proven that the documents specified in the first sub-clause cannot be submitted, the inspection report drawn up by the responsible manager of the finished product manufacturing site in accordance with the second paragraph of Article 14 of the Regulation on the Manufacturing Plants of Medicinal Products for Human Use, and the declaration accepted by the Agency.

ş) Document, issued by the Agency, belonging to manufacturing site for all manufacturing steps of finished medicinal products for human use other than the products that are deemed appropriate to be submitted after the marketing authorization application in the assessment made by the Priority Assessment Committee or for manufacturing steps for which document is not issued by the Agency, document accepted by the Agency, issued by a competent health authority showing that manufacturing is made in accordance with the good manufacturing practices guidelines or where this document is not physically issued, particular and document accepted by the Agency showing that manufacturing is made in accordance with the good manufacturing practices guidelines or document issued by the official authorities of the countries that have mutual recognition agreements with Turkey showing that they can

manufacture within the framework of good manufacturing practices or for medicinal products for human use to be manufactured in Turkey, manufacturing site authorization.

t) In case the applicant is not a manufacturer of medicinal products for human use to be manufactured in Turkey, the contract for contract manufacturing with a manufacturer that meets the conditions set forth in the Regulation on Manufacturers of Medicinal Products for Human Use and the registration certificate of the parties.

u) In the case of a product that is imported or manufactured on license for which an application is pending, list of other country/countries where an authorization application for the product is pending, and a copy of the authorization certificate approved by health authorities from any of the listed countries before authorization is granted in Turkey, or in cases where these documents are not issued, information or document showing the product's authorization has been approved by the relevant authority and accepted by the Agency.

ü) In the event that the product for which a marketing authorization 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 name of the medicinal product for human use in question in the country in question, the date of the transactions conducted and the relevant justification of such transaction.

v) In addition to the documents sought within the scope of this article in the marketing authorization application of a radionuclide generator, the detailed description of the system and the components that make up the system that may affect the quality and composition of the daughter nuclide preparation, and the qualitative and quantitative details of the eluate or sublime.

y) Summary of product characteristics prepared in accordance with Article 10, package leaflet, mock-ups of the outer packaging of the medicinal product for human use in the size and form to be placed on the market prepared in accordance with the Regulation on Labelling, Package Leaflet and Tracking of Medicinal Products for Human Use published in the Official Gazette dated 25/4/2017 and numbered 30048, in the case of a medicinal product for human use imported or manufactured on license, if any, summary of product characteristics, package leaflet, mock-ups of outer packaging of current reference medicinal products for human use approved by the competent authorities of the other country or countries where the product is placed on the market and, if any, showing the approval date.

z) Documents related to pharmacovigilance that must be submitted during the marketing authorisation application in line with the Regulation on the Safety of Medicines published in the Official Gazette dated 15/4/2014 and numbered 28973.

aa) The document defining the science service and the address, KEP address, telephone and fax number of this service within the scope of the Regulation on Promotional Activities of Medicinal Products for Human Use published in the Official Gazette dated 3/7/2015 and numbered 29405.

bb) Where applicable; documents showing that the medicinal product for human use, for which a marketing authorisation application is submitted, meets the requirements specified in Articles 33 or 36.

cc) Evaluation of the potential environmental risks posed by the medicinal product for human use.

(2) All official documents obtained from abroad shall be annotated with apostille or approved by the consulate. It is essential that all documents shall be submitted in Turkish. Parts deemed appropriate by the Agency may be presented in English. However, those prepared in languages other than English shall be submitted with a sworn Turkish translation. In cases where sworn translation cannot be made in Turkey, a sworn translation document translated into Turkish or English in another country may be accepted.

(3) Detailed summaries of the documents related to the results of physicochemical, biological or microbiological tests, preclinical tests and clinical studies specified in subparagraphs (j), (k) and (l) of the first paragraph, prepared in accordance with Article 11, shall be submitted.

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

(5) Authorization in subparagraph (r) of the first paragraph; does not remove the legal responsibilities of the applicant or marketing authorisation holder.

Informed consent application, established medical use application, allergen product application, generic medicinal product application, hybrid application, biosimilar medicinal product application, fixed combination application

ARTICLE 9 – (1) Without prejudice to the provisions of the Industrial Property Law dated 22/12/2016 and numbered 6769;

a) The applicant shall not be required to provide the results of toxicological and pharmacological tests and clinical trials provided that the he proves one of the following:

1) In the informed consent application made where the marketing authorization holder of the reference medicinal product shall have consented to the use of the pharmaceutical, pre-clinical and clinical documentation contained in the dossier of the reference medicinal product for the purpose of evaluating the referred application and the medicinal product for human use, for which the registration application has been applied, is essentially in the same qualitative and quantitative composition and in the same pharmaceutical form with a medicinal product previously authorised in Turkey,

2) In the established medical use application for which appropriate scientific literature is submitted instead of the results of pre-clinical tests and clinical studies in Annex-1, where the active substance(s) of the medicinal product for human use, for which a marketing authorisation application has been applied for, has a well-established medical use with acceptable efficacy and safety, which is determined to have been used for at least ten years in any country accepted in the product-based evaluation by the Agency, prior to the marketing authorisation application through the detailed scientific literature,

3) In the application in which the efficacy and safety of the allergen product for which the marketing authorisation application is made, for the indication and route of administration, is proven by referring to the published literature or the reference medicinal product,

4) In the case of an generic medicinal product application to be made in the event that the medicinal product for human use for which the marketing authorisation application has been made, is basically similar to a reference medicinal product that has been authorised in accordance with the current legislative provisions and has completed its data exclusivity period,

in the implementation of sub-paragraph (4), data exclusivity shall be valid for reference medicinal products to be authorised for the first time after 1/1/2005 in one of the countries in the Customs Union Area and its duration shall be six years, starting from the date it was first authorised in the Customs Union Area. With regard to those products which benefit from patent protection in Turkey, the implementation of the data exclusivity period of six years shall be limited to this patent period.

b) Hybrid application shall be made in cases where the definition of generic medicinal product for human medicinal product is not fully met or where the bioequivalence cannot be demonstrated through bioavailability studies or in case of changes in the active substance(s), 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 must be submitted at the time of this application.

c) Where a biological medicinal product for which a marketing authorisation application is submitted and does not meet the conditions in the definition of generic medicinal products,

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 must be provided. The type and quantity of supplementary data to be provided must comply with the relevant criteria stated in Annex I and the related guidelines published by the Agency. The results of tests and clinical trials from the reference medicinal product's dossier shall not be provided.

ç) In the fixed combination application made for medicinal products containing active substance(s) used in the composition of medicinal products for human use authorized in Turkey and that are used in combination for therapeutic purposes, in addition to the appropriate bioavailability or bioequivalence data, literature data showing that the said active substance(s) are effective and safe when used in combination and retrospective studies with data collected from hospitals in Turkey, if any shall be provided. If the submitted studies are found to be insufficient by the Agency, it is obligatory to submit the results of the clinical studies conducted with the new combination and the scope of which is determined by the Agency.

d) In the fixed combination application made for medicinal products containing active substances used in the composition of medicinal products for human use authorised in the world but not used in combination for therapeutic purposes, it is obligatory to submit the results of clinical studies related to this combination and, where necessary, preclinical tests. However, it is not necessary to provide scientific references for each active substance unless requested by the Agency.

Summary of product characteristics

ARTICLE 10 – (1) The summary of the product characteristics shall be presented including the following information:

a) Name, strength, pharmaceutical form of the medicinal product for human use.

b) The qualitative and quantitative composition of the active substance/substances contained in the human medicinal product, using common names, and in case of excipients that should be included in this section, qualitative and quantitative information about those substances. In cases where animal source is used in the active substance(s) and excipients of the medicinal product for human use, this source shall be included.

c) Pharmaceutical form.

d) Clinical particulars:

1) Therapeutic indications,

4.2 Posology and method of administration

3) Contra-indications,

4) Special warnings and precautions for use and, 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) Interaction with other medicinal products and other forms of interaction,

6) Use during pregnancy and lactation,

7) Effects on the ability to drive and use machines,

8) Undesirable effects,

9) Overdose and its treatment.

d) Pharmacological properties:

1) Pharmacodynamic properties,

2) Pharmacokinetic properties,

3) Preclinical safety data.

e) Pharmaceutical particulars:

1) List of excipients,

2) Incompatibilities,

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

4) Special precautions for storage,

5) Nature and contents of container,

6) Special precautions for disposal of a used medicinal product for human use or waste materials derived from such medicinal product, if appropriate.

f) Marketing authorisation holder.

g) Marketing authorisation number.

ğ) Date of marketing authorisation number.

h) Date of renewal of summary of product characteristics.

ı) For radiopharmaceuticals, full details of radiation dosimetry.

i) For radiopharmaceuticals, additional detailed instructions for reparation and quality control of such preparation and, where appropriate, maximum storage time during which any intermediate preparation such as an eluate or the ready-to-use pharmaceutical will conform with its specifications.

j) Requirements specified in the Regulation on the Safety of Medicines.

Expert reports

ARTICLE 11 – (1) While making an application to the Agency, the applicant shall submit the expert reports signed by the relevant experts for each of the chemical, pharmacological, biological, toxicological and clinical parts of the marketing authorisation dossier.

(2) The duties of the experts who will prepare the reports shall be as follows in accordance with their qualifications:

a) To perform their duties within their own disciplines such as 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-1 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 toxicity and pharmacological properties of the medicinal product for human use,

3) In case of clinicians, to specify whether the particulars and documents presented to the Agency 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, contra-indications and adverse effects,

(3) 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 application should be specified where necessary.

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

SECTION THREE
Evaluation of the Application for Marketing Authorization and Granting of Marketing Authorization

Pre-Assessment of the Application

ARTICLE 12 – (1) Marketing authorisation applications can be made by applicants throughout the year. Marketing authorisation granting process, on the other hand, can only be started in February, May, August and November, taking into account the marketing authorisation granting capacity of the Agency.

(2) The issue of whether the application file submitted to the Agency to obtain a marketing authorisation for a medicinal product for human use is a complete application in terms of the documents to be submitted according to the nature of the application and the electronic marketing authorisation application requirements shall be examined by the Agency, subject to preliminary assessment. This assessment shall be made in the order of application date. However, the preliminary assessment procedures of the applications that are deemed appropriate to be assessed as priority or high priority in the marketing authorisation procedures by the Agency's Priority Assessment Committee are made with priority.

(3) Necessary assessment shall be made within thirty days after the application dossier reaches the Agency and the result shall be notified to the applicant. In case of deficiencies in the application dossier, the applicant shall complete these within thirty days. The second preliminary assessment to be made after the deficiencies are completed and submitted to the Agency is concluded within thirty days.

Procedural rejection of the application

ARTICLE 13 – (1) In the cases listed below, the application shall be rejected due to the procedure and returned to the applicant;

a) Failure to complete the deficiencies regarding the first preliminary assessment made by the Agency within the scope of Article 12 and not making the second application within the time limit, or failure to complete the deficiencies regarding the first preliminary assessment in the second preliminary assessment application,

b) Failure to pay the marketing authorisation fee within sixty days after the official notification to the applicant that the marketing authorisation process has been completed,

c) Failure to submit the information and documents requested by the Agency, apart from the preliminary assessment process, or the necessary explanation regarding the failure to submit such information and documents, together with the date of submission, within thirty days at the latest, to the Agency.

Period of marketing authorization process

ARTICLE 14 – (1) During the preliminary assessment, the Agency shall examine the marketing authorisation application according to the marketing authorisation criteria and officially notifies the applicant that the application has been accepted or rejected. The notification that the application has been accepted shall not be considered as the beginning of the marketing authorization period. For the complete marketing authorisation applications that have been accepted after the assessment has been completed the marketing authorisation holder shall also be notified by the Agency that the marketing authorisation granting process has started. The date of this notification shall be considered as the start date of the marketing authorization granting process. The marketing authorization granting shall be finalized within the next two hundred and ten days. In addition, the time elapsed for the testing of starting materials, intermediate products and other ingredients of the medicinal product for human use in the Agency's laboratory or in a laboratory designated by the Agency for this purpose in order to determine the declared accuracy of the control methods employed by the manufacturer in the production of the human medicinal product and defined in the documents submitted in the application pursuant to subparagraphs (i) and (j) of the first paragraph of Article 8; the time elapsed for the assessment of external institutions; the time elapsed for public holidays except for the weekends and emergency situations shall not be included in the marketing authorization granting period.

(2) In the case of marketing authorisation application for co-marketed products, only the Module 1 part of the marketing authorisation application dossier made with the full and complete dossier, prepared in accordance with Annex-1, shall be examined and the marketing authorisation granting period of two hundred and ten days shall be ninety days for these applications. A marketing authorisation application can also be made only with Module 1

prepared in accordance with Annex-1. For co-marketed product marketing authorisation applications made in this way, other modules cannot be submitted during the marketing authorisation granting process and after granting marketing authorisation.

(3) In cases where necessary, additional particulars and documents are requested from the applicant by the Agency within the scope of Articles 8, 9, 10, 33 and 36 during the marketing authorization process, the marketing authorization process shall suspended until the relevant particulars and documents have been provided.

Prioritization in marketing authorization processes

ARTICLE 15 – (1) Marketing authorization procedures shall be carried out over electronic systems according to the start date of the marketing authorization process. However, the applications of products applied for according to the Articles 8, 9, 33 or 36 that are approved by the Agency's Priority Assessment Committee, shall be assessed as priority in the marketing authorisation procedures.

(2) The marketing authorisation granting procedures of products in this case shall be completed within the periods specified in the prioritization guideline published by the Agency.

(3) The provisions in the first and third paragraphs of Article 14 regarding the suspension of the period shall also apply for the medicinal products for human use determined within the scope of this article.

Marketing authorization criteria

ARTICLE 16 – (1) The criteria to be taken into account by the Agency regarding the product while issuing a marketing authorisation for a medicinal product for human use are as follows:

a) The quality has been demonstrated by appropriate technological and pharmaceutical properties.

b) Proven effectiveness under the proposed conditions of use.

c) Proven safety.

Assessment of applications

ARTICLE 17 – (1) The following aspects shall be taken into consideration while assessing the applications:

a) Scientific and technological examination of documents proving the efficacy, safety and quality of a product.

b) In order to determine the applicability of the methods according to the pharmacopoeia method and specifications used by the manufacturer during the control of the product, if not available, according to the company's method and specification and the accuracy of the formulation of the medicinal product for human use has been tested in the Agency's laboratory or in a laboratory designated by the Agency for this purpose,

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

Refusal of the application on fundamental grounds

ARTICLE 18 – (1) The medicinal product for human use for which a marketing authorisation application has been made shall be subjected to analysis. In case of any non-conformity in the first analysis, the analysis shall be repeated by requesting the corrected sample from the company. In the second analysis, in case of nonconformity, an assessment meeting shall be hold with the representatives of the company about the analysis method and the analysis method of the new sample shall be determined and the analysis is performed. In the third analysis, if there is any nonconformity, a final evaluation meeting shall be hold with the representatives of the company, the nonconformity of the analysis is described and the new analysis method shall be determined and the analysis shall be conducted for the last time. In cases where that the qualitative and quantitative formula nonconformity is determined and the

declared specifications are outside the acceptable limits, although the specified analysis steps are completed, the marketing authorisation application shall be rejected on fundamental grounds.

(2) As a result of the evaluation of the documents and information submitted after the applicant is given the right of maximum three written and two verbal answers for each of the following situations of the evaluation process of the application made to the Agency for the marketing authorisation of a human medicinal product the application shall be rejected on fundamental grounds;

a) Under normal conditions of use, the potential risk is greater than the beneficial effect of the treatment, or

b) Its therapeutic effect is insufficient or its therapeutic effect has not been sufficiently proven, or

c) If applicable, its bioavailability is not sufficient, or

ç) In applications for biosimilar medicinal products, similarity to the reference biological product cannot be proven,

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Notification of refusal of the application on fundamental grounds, and objection

ARTICLE 19 – (1) In case of refusal of the marketing authorization application, this decision shall be communicated to the applicant with the relevant justification, or if the notification cannot be made, it can be announced on the website of the Agency. The applicant shall hold the right to submit a written objection to the decision within forty-five days from the date of notification or announcement. In the event no objection is submitted within forty-five days, the application documents shall be returned to the applicant. In case the applicant does not receive the documents back; the provisions of the Regulation on State Archive Services dated 18/10/2019 and numbered 30922 shall apply.

(2) The objection submitted shall be evaluated by the Agency 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.

(3) The decision made as a result of the evaluation of the objection is final and no objection can be made to the Agency regarding the said decision.

(4) The rejection of the application on the merits shall not prevent the applicant from reapplying for marketing authorization.

Granting marketing authorization

Article 20- (1) As a result of examination and evaluation of the information and documents submitted by the applicant to the Agency, the medicinal product for human use determined to be in compliance with the aspects envisaged by this Implementing regulation shall be drafted and the applicant shall be duly informed.

(2) With the exception of only aroma difference and only single-dose multidose usage difference for lozenges, oral sprays, chewable tablets, fish oil preparations, nicotine gums and pediatric vitamin syrups; a second marketing authorization shall not be granted to the same natural or legal person, even with a different trade name, for a medicinal product for human use granted marketing authorization by the Agency for a product with the same qualitative and quantitative composition in unit dose, in the same indication and in the same pharmaceutical form. However, applications for a medicinal product for human use that are scientifically and technologically proven to be superior to an authorized medicinal product for human use are separately evaluated by the Agency. In the evaluation regarding the acceptance of the active substance(s) as the same within the scope of this paragraph, subparagraph (i) of the first paragraph of Article 4 is taken as the basis.

(3) The same natural or legal person cannot use a different trade name for medicinal products for human use with the same active substance/s and indications, different strengths or route of administration or pharmaceutical forms.

(4) A medicinal product for human use cannot be given a marketing authorization with the same name as a traditional herbal medicinal product or a homeopathic medicinal product.

(5) Marketing authorizations, certificates and other internationally valid documents may also be prepared as physical documents by the Agency.

(6) The list of medicinal products for human use authorized by the Agency is announced on the official website of the Agency at least once a month and in the Official Gazette once a year.

Validity period of marketing authorizations

ARTICLE 21 – (1) The evaluation regarding the renewal of the marketing authorization is made by the Agency five years after the date of issue, taking into account the benefit/risk balance. In accordance with the provisions of the Regulation on the Safety of Medicines, the marketing authorization holder shall submit the file containing all up-to-date information on efficacy, safety and quality, including the evaluation of suspected adverse reaction reports and periodic benefit/risk evaluation reports, and information on all variations of the product since its registration to the Agency nine months before the expiry of the five-year period.

(2) Once the marketing authorization is renewed, the marketing authorization is valid indefinitely, unless the Agency decides to carry out an additional five-year renewal assessment for pharmacovigilance-related reasons, including insufficient patient exposure to the relevant medicinal product for human use.

(3) In cases where five-year pharmacovigilance data regarding the product cannot be submitted due to the fact that it has not been put on the market, the evaluation regarding the validity of the marketing authorization is made after the current pharmacovigilance data is prepared and submitted in accordance with the provisions of the relevant legislation.

Suspension of marketing authorization

ARTICLE 22 – (1) Regarding a authorized product; in case of detection of at least one of the below conditions:

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

b) Determining that it has no or insufficient therapeutic effect,

c) Producing with a formula different from the formula that is the basis for the marketing authorization,

ç) Making changes in the formula, strength, pharmaceutical form, packaging and short product information based on the marketing authorization without the knowledge or approval of the Agency,

d) 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 for human use according to generally accepted scientific methods and to present them to the approval of the Agency,

e) 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,

f) It is determined that the production method and control methods used by the producer in sub-paragraphs (g) and (i) of the first paragraph of Article 8 are not applied as specified,

g) Failure to comply with the provisions of the legislation regarding the packaging information and the instructions for use,

ğ) Failure to make or notify necessary updates in short product information and instructions for use,

h) The marketing authorization holder does not respond to the Agency's instructions regarding the medicinal product for human use within the time specified by the Agency,

ı) In accordance with the provisions of this Regulation, it is determined that there are errors in the documents submitted in the application for a medicinal product for human use that will affect the quality, effectiveness or safety of the product, or the documents submitted become invalid,

i) Provided that it is approved by the Agency, except for the cases where it is not produced for a single country market or cannot be offered to the market in our country due to the size of the commercial series; at least one commercial batch of a medicinal product for human use has not been placed on the market within the first thirty months from the date of registration,

j) At least one commercial batch of an authorized medicinal product for human use manufactured in our country and previously on the market within the scope of data matrix application, in domestic or foreign markets for an uninterrupted thirty months; for products imported to our country, it is determined that they are not in the domestic market or the official documents showing that they are on the market for medicinal products for human use outside the scope of data matrix application are not submitted to the Agency,

k) Deciding to suspend the marketing authorization as a result of the benefit/risk assessment made by the Agency for notifications received within the framework of pharmacovigilance practices,

l) Determining the situations that require the suspension of the marketing authorization in accordance with the provisions of the Regulation on the Safety of Medicines,

m) Failure to fulfill the obligation in the first paragraph of Article 25,

n) Failure to fulfill the commitments in subparagraph (c) of the first paragraph of Article 26,

o) The medicinal product for human use, which is important for the sustainability of public health and access to the medicine, is not placed on the market by the marketing authorization holder within six months from the date of request, despite the request by the Agency,

the marketing authorization of the medicinal product for human use is suspended by the Agency.

(2) The production or import of the medicinal product for human use, the marketing authorization of which is suspended, for placing on the market is stopped. Medicinal products for human use that have already been imported or produced cannot be placed on the market unless the Agency decides otherwise. The decision on medicinal products for human use on the market is taken by the Agency, taking into account the reason for the suspension of the marketing authorization.

(3) The Agency may make an exception to the application of subparagraphs (i) and (j) of the first paragraph for medicinal products for human use, which may cause serious public health problems if they are not ready for use or are not needed at all in our country's market but are exported.

(4) The list of medicinal products for human use whose marketing authorization has been suspended is announced on the official website of the Agency.

(5) In case the products whose marketing authorization have been suspended for the reasons specified in subparagraphs (i) or (j) of the first paragraph are desired to be placed on the market again, an application is made to the Agency for the suspension of the marketing authorization, with a commitment to put the product on the market within six months at the latest, in accordance with the procedures determined by the Agency. If approved by the Agency, the product marketing authorization is suspended. For products that are not placed on the market within the promised period, a transaction is established in accordance with Article 23.

Cancellation of marketing authorization

ARTICLE 23 – (1) In the presence of one of the following conditions, the marketing authorization granted for a medicinal product for human use is revoked:

a) Except for those listed in subparagraphs (i) and (j) of the situations listed in the first paragraph of Article 22, failure to submit documents proving the opposite of the reason for suspension by the marketing authorization holder within six months at the latest from the date of suspension of the marketing authorization or the documents explaining the situation not being approved by the Agency.

b) The marketing authorization holder's request and the Agency's approval, provided that there is no attachment or injunction notified to the Agency on the marketing authorization.

c) The products are not placed on the market within the promised period pursuant to the fifth paragraph of Article 22.

(2) In case the marketing authorization of the product for which the application is made with a full and complete file is revoked, the marketing authorizations of the co-marketed products whose marketing authorization application was accepted only with Module 1 prepared in accordance with Annex-1 are also revoked.

(3) The production or import of a medicinal product for human use whose marketing authorization has been revoked is stopped. The decision on medicinal products for human use currently on the market is taken by the Agency, taking into account the reason for the cancellation of the marketing authorization.

(4) Marketing authorization whose cancellation process is deemed appropriate and suspended according to subparagraph (b) of the first paragraph is announced on the official website of the Agency for a period of six months. Marketing authorization in this situation is transferred, upon request, to real or legal persons who undertake to place the product on the market and meet the conditions for applying for a marketing authorization set forth in this Regulation, provided that the application conditions for the transfer of marketing authorization are met, upon the request of these persons and the consent of the marketing authorization holder. Cancellation of marketing authorization for which transfer application has been made will not continue.

(5) In case the products for which the marketing authorization cancellation is requested according to subparagraph (b) of the first paragraph is a medicinal product for human use that is marketed jointly and the marketing authorization application is made with a complete and complete file, it is obligatory for the marketing authorization holder to submit the list of other medicinal product/products for human use subject to co-marketing to the Agency.

(6) The marketing authorization suspension period of the products suspended pursuant to subparagraph (o) of the first paragraph of Article 22 may be extended for another six months if deemed appropriate by the Agency.

(7) The list of medicinal products for human use whose marketing authorization has been revoked by the Agency is announced on the official website of the Agency.

Loss of marketing authorization or product files

ARTICLE 24 – (1) In case the marketing authorization given by the Agency is lost, the marketing authorization holder shall apply for lost marketing authorization to the Agency with a newspaper advertisement showing that the marketing authorization is lost. In this case, a new marketing authorization is issued.

(2) In case the marketing authorization file of the medicinal product for human use for which a marketing authorization application has been made is lost, an application for a lost marketing authorization file is made to the Agency by the applicant or the marketing authorization holder. A copy of the file is given to the applicant for applications whose justification is approved by the Agency.

The responsibility of the marketing authorization holder

ARTICLE 25 – (1) If the marketing authorization holder cannot place a product on the market for any reason, he is obliged to notify the Agency that he will not be able to place the product on the market at least thirty days before this situation occurs.

(2) The marketing authorization holder is responsible to the Agency for the following matters regarding the medicinal product for human use for which it has a marketing authorisation:

a) Production of the medicinal product for human use in accordance with the specifications given in the annex of the application and accepted by the Agency.

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

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

ç) When there is any change regarding the medicinal product for human use, notifying the Agency of the relevant change within the framework of the provisions of the relevant guideline.

d) Responding to the issues requested by the Agency regarding the medicinal product for human use in a timely manner.

e) Fulfilling the obligations specified in the Regulation on the Safety of Medicines within the framework of pharmacovigilance practices.

f) To take the necessary measures to prevent the infections that can be transmitted in case the medicinal product for human use is a biological medicinal product.

g) Ensuring the market availability of the medicinal product for human use for which it has a marketing authorisation.

ğ) In case the marketing authorization of the medicinal product for human use is suspended or withdrawn from the market due to its effectiveness or protection of public health, immediately notifying the Agency with all the details of any measures taken.

h) Notifying the Agency of the suspension or cancellation of the marketing authorization in other countries where it is authorized, of withdrawal from the market or recall of medicinal products for human use, which are imported, exported or produced in our country under license, due to quality, efficacy or safety.

ı) Payment of determined fees and charges related to medicinal products for human use.

(3) The marketing authorization holder or the applicant is obliged to make an application in accordance with the principles set forth in this Regulation and to confirm the accuracy of the information and documents submitted to the Agency, and accepts all kinds of responsibility arising from the results of such information and documents.

(4) The marketing authorization holder or the applicant is responsible for keeping the originals of all documents submitted to the Agency regarding the product and submitting them to the Agency when requested.

(5) The fact that the medicinal product for human use is authorized does not affect the legal and penal liability of the marketing authorization holder.

Transfer of marketing authorization

ARTICLE 26 – (1) The registration of a medicinal product for human use authorized by the Agency can be transferred. The following documents are submitted to the Agency for marketing authorization transfer procedures:

a) The court decision stating that the marketing authorization has been transferred by the court, the decision of the enforcement office regarding the sale of the marketing authorization through forced execution, or the contract drawn up in the presence of a notary public and containing the following issues;

1) The name, registration date and number of the medicinal product for human use subject to the marketing authorization transfer process,

2) Names and addresses of real or legal persons who will transfer the marketing authorization and take over the marketing authorisation,

3) A report stating that the current medicinal product for human use file approved by the Agency, complete and updated, has been delivered to the transferee in full.

b) Demonstrating that the person transferring the marketing authorization can fulfill all the responsibilities expected from the marketing authorization holder;

1) For those who can apply for a marketing authorization in Article 7, the original or notarized copy of the diploma showing that they belong to one of the professions specified, or a graduation certificate from the Higher Education Council,

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

3) Documents related to the pharmacovigilance officer within the scope of the Regulation on the Safety of Medicines,

4) The document defining the science service within the scope of the Regulation on Promotional Activities of Medicinal Products for Human Use and the address, telephone number and KEP address of this service.

c) Name, surname, address, telephone number and KEP address of the person who has taken over the marketing authorisation, updated brief product information of the medicinal product for human use, instructions for use, a copy of the inner and outer packaging, and in the transfers made through a notary public, the original of the previous marketing authorization for the product in question; where updated brief product information and leaflet cannot be provided, a fully prepared undertaking by the transferee, stating that all necessary changes and updates regarding the short product information and instructions for use of the medicinal product for human use will be made in line with the relevant guidelines after the registration transfer process of the human medicinal product is completed, and that no sales permit application will be made without obtaining approval,

ç) In the case of an imported product, a document showing that the importing real person or legal entity is the sole representative authorized for importing, marketing authorization and selling the product in Turkey, and in the case of co-marketing, a document issued by the licensor showing that a real person or legal person other than the sole authorized representative in Turkey is also granted co-marketing authorization and written approvals of natural or legal persons who will do joint marketing with the company,

d) In the case of a product manufactured on license, a document issued by the licensor showing that the real person or legal entity manufacturing the product is the sole authorized representative that can manufacture and sell the product in Turkey, and in the case of co-marketing, a document issued by the licensor showing that a real person or legal person other than the sole authorized representative in Turkey is also granted co-marketing authorization and written approvals of natural or legal persons who will do joint marketing with the company,

e) If the applicant is not a manufacturer of medicinal products for human use to be manufactured in Turkey, the contract for contract manufacturing with a manufacturer that meets the conditions specified in the Regulation on Manufacturing Plants of Medicinal Products for Human Use.

(2) In addition to the documents listed in the first paragraph, the following matters are valid for transfers made through a notary public:

a) A letter of undertaking prepared by the transferee company stating that no changes have been made regarding the medicinal product for human use during the transfer application must be submitted.

b) After the realization of the transfer transaction, in case a full undertaking prepared by the transferee company stating that all necessary changes and updates will be made regarding the medicinal product for human use, necessary updates regarding the existing product file and actions to correct the deficiencies, if any, are carried out after the registration transfer of the medicinal product for human use, in line with the relevant guidelines, and a sales permit cannot be applied without obtaining approval.

c) In case of demand; with the condition of a written and notarized agreement of the companies that transfer and take over the marketing authorisation, the products with old barcodes are allowed to be produced and put on the market only by the transferee company for a period of six months after the new marketing authorization is issued. Control processes regarding the production notifications of the products in this situation are carried out through the Pharmaceutical Track and Trace System. These products can be found in the market until their expiration date. The supply of the transferred products to the market is stopped by the transferring company. Products with old barcodes can be imported by the transferor company for a period of six months after the new marketing authorization is issued, provided that the companies that transferred and took over the marketing authorization have a written and notarized agreement. However, these products may be offered to the market on the condition that the transferring company makes a production notification to the Pharmaceutical Track and Trace System and the products are transferred to the transferring company via the Pharmaceutical Track and Trace System.

(3) In case the licensor changes the natural or legal person authorized for the licensing/sales/production of the product in question in Turkey, in addition to the documents listed in the first paragraph of this article, submission of the current marketing authorization holder's letter stating that he has returned the original marketing authorization is required; when a court decision is presented showing that the current marketing authorization holder has no authority, all the requirements in this article must be fulfilled together with the Module 1 file prepared in accordance with Annex-1 of the medicinal product for human use, except for subparagraph (a) of the first paragraph. However, if the product in this situation is the only diagnosis or treatment option for disease in our country, the Agency may accept and conclude the transfer application for the license/permit or registration certificate without waiting for the court decision.

(4) The Agency evaluates the marketing authorization transfer application within thirty days.

Transfer of marketing authorization application

Article 27 - (1) Any real person or legal entity applying for authorization may transfer or assign all its rights arising from such application to another real person or legal entity, provided all requirements set out in Article 26 must be fulfilled.

Obtaining sales permit

ARTICLE 28 – (1) Pursuant to the provisions of this Regulation, it is obligatory to obtain a sales permit for the medicinal product for human use that will be authorized by the Agency and put on the market for the first time.

(2) The marketing authorization holder submits the document issued by the Agency to the Agency, in case of carrying out the storage activities for the medicinal products for human use, for which the sale price application to the warehouse is approved by the Agency, in the facilities belonging to its own private or legal entity, in other cases, it submits the document issued by the Agency regarding the storage place, the document signed between the parties regarding the storage of the product and the registration certificate of the parties to the Agency together with the sales permit application.

(3) The Agency examines all printed materials regarding the medicinal product for human use for which the sales permit is applied, in terms of necessary information.

(4) It is not necessary to obtain a resale permit for transactions that cause changes in the packaging information or specifications of the medicinal product for human use, or in the instructions for use. However, after the transfer of the production site from abroad to our country or from our country to abroad, packaging size change, marketing authorization transfer procedures and before the products whose marketing authorization is suspended in accordance with the fifth paragraph of Article 22 are put on the market; a sales permit must be obtained by applying to the Agency together with the documents specified in the second paragraph.

Permit of human blood products to be placed on the market

ARTICLE 29 – (1) For human blood products with a sales permit, for which a permit has been applied for or for which a marketing authorization has been applied, the license/permit holder applies to the Agency to obtain a market release permit for each batch of the product, in addition to the issues set forth in Article 28, before placing the product on the market.

(2) Before the permit for placing on the market, the analyzes determined according to the product for each batch of human blood products or medicinal products for human use containing human blood products and for each plasma pool used in these batches must have been performed in the Agency's laboratory or in a laboratory accepted by the Agency for this purpose. However, in cases where the human blood product is not included as an active substance in the content of the medicinal product for human use and the reasons for not providing the plasma pool are approved by the Agency; The analyzes determined according to the product for each batch of medicinal product for human use, without looking for plasma pool analysis, must be performed in the Agency's laboratory or in a laboratory accepted by the Agency for this purpose.

(3) In order to obtain a permit for placing on the market for human blood products or medicinal products for human use containing blood products, the amount requested to be offered for sale and the documents and information specified below are submitted to the Agency and the analyzes made in accordance with the second paragraph and the aforementioned documents are approved by the Agency, the relevant medicinal products for human use are permitted to be placed on the market:

a) Name and content of the medicinal product for human use,

b) Serial release certificate issued by an accredited national or international laboratory for each batch of bulk or finished product (if the document is obtained from abroad, apostille annotated/consulate approved),

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

ç) A document showing the amount of products sold, issued by the marketing authorization holder and, where applicable, by the licensor company, showing in which countries each batch is sold or, in cases where the entire batch is imported to our country, in which countries/countries the other products in which the plasma pools used in the relevant series are used are sold,

d) The rules based on plasma donation, the date of collection of plasma and the donor type (volunteer, paid) and the list of donors when necessary,

e) The document given by the accredited national or international laboratory stating that the HBsAg, HIV 1/2 and HCV RNA tests of the samples belonging to each plasma pool were applied and the results,

f) For each series, a document issued by the manufacturer stating that the donors are safe in terms of diseases or suspected diseases determined by the Agency (for example, Creutzfeld-Jacob (CJ) disease) and that there are no donors with these diseases among the donors,

g) The up-to-date variation commitment for the product with the serial number of which is issued by the licensee and, where applicable, the licensor.

(4) In the case of medicinal products for human use, which are intended to be imported as bulk products of blood products and put on the market by producing the finished product in

our country, the original document, issued by the marketing authorization holder and, where applicable, the licensor company, showing the country(s) where the other products using plasma pools used in bulk products are authorized /produced and in which country(s) they are sold, must be submitted to the Agency for each batch of the bulk product to be imported, in addition to the issues in subparagraphs (a), (b), (c), (d), (e), (f) of the third paragraph. Provided that all documents are submitted within the scope of this paragraph for human blood products imported in bulk and produced in our country and authorized and sales permit in this direction, the analyzes made in accordance with the second paragraph and the relevant information and documents are approved, only if the commitment stated in subparagraph (g) of the third paragraph is submitted, the permit for placing on the market is granted.

Permit for immunological medicinal products for human use to be placed on the market

ARTICLE 30 – (1) With the exception of allergen products, for authorized or authorized immunological medicinal products for human use for which a marketing authorization application has been made; the marketing authorization/permit holder applies to the Agency to obtain a marketing authorization for each batch of the product before placing its product on the market.

(2) Before the permit for the immunological medicinal products for human use to be placed on the market for which a marketing authorization application has been made, analyzes determined according to the product must have been carried out in the Agency's laboratory or in a laboratory accepted by the Agency for this purpose.

(3) In order to obtain a permit for immunological medicinal products for human use to be placed on the market for which a marketing authorization application has been made or authorized, the amount requested to be placed on the market is notified and the following documents and information are submitted to the Agency:

a) For each batch, batch/lot release certificate issued by an accredited national laboratory or international laboratory for the bulk or finished product (if the document is obtained from abroad, apostille annotated/consulate approved),

b) The original of the analysis certificate approved by the technical manager of the production center for each batch,

c) The current variation commitment for the product to be imported and whose serial number is specified, issued by the licensor firm and the marketing authorization holding firm.

(4) For immunological medicinal products for human use, for which a marketing authorization application has been made or authorized, the documents submitted within the scope of the application and the results of the analysis of the approved products for which a marketing authorization has been applied, shall be allowed to be placed on the market for the relevant batch.

Post-marketing authorization variations

ARTICLE 31 – (1) With the exception of Article 26, after the marketing authorization of a medicinal product for human use, an application is made to the Agency by the marketing authorization holder in accordance with the provisions of the relevant regulation and guideline for all changes regarding this product.

(2) In case of an application, the Agency may give scientific advice to the applicant after the medicinal product for human use is authorized, subject to a fee included in the price schedule.

SECTION FOUR
Conditional and Exceptional Marketing Authorization

Detection of specific cases

ARTICLE 32 – (1) The determination of the specific case regarding the conditional and exceptional marketing authorization requirement for medicinal products for human use is made

by the Priority Evaluation Board. As a result of the evaluation made by the Priority Evaluation Board, an application is made to the Agency in accordance with Article 33 or 36 for medicinal products for human use, which are found suitable for a conditional or specific marketing authorization application.

Conditional marketing authorization (emergency use authorization) application

ARTICLE 33 – (1) Except for changes related to changes in the therapeutic indications of an authorized medicinal product for human use or adding new ones, a conditional marketing authorization application can be made to the Agency for medicinal products for human use that fall under at least one of the following:

a) Medicinal products for human use which aim the treatment, prevention or the medical diagnosis of severely debilitating diseases or life-threatening diseases;

b) Medicinal products for human use that to be used in emergency situations, in response to public health threats duly recognized by the World Health Organization or the European Union or accepted by the Ministry of Health.

(2) Although comprehensive clinical data on efficacy and safety are not yet available, conditional authorization may be granted if all of the following requirements are met:

a) The benefit/risk balance of the medicinal product for human use is positive,

b) The applicant's ability to provide comprehensive clinical data,

c) Elimination of unmet medical need,

ç) Although it requires additional data, the public health benefit provided by the availability of the relevant medicinal product for human use on the market is greater than the risk posed by its absence.

(3) The unmet medical need specified in subparagraph (c) of the second paragraph means that there is no medical diagnosis, disease prevention or treatment method that adequately meets this need in our country, or even if there is a method that meets the need, this method will provide a great advantage in treatment for patients.

(4) Applications to be made within the scope of this article are made in accordance with the guideline published by the Agency.

Assessment of conditional marketing authorisation (emergency use authorization) applications, duration and renewal of conditional authorization

ARTICLE 34 – (1) For the medicinal product for human use for which a conditional authorization application has been made in accordance with Article 33, under the following conditions; authorizing is done or marketing authorizations are renewed.

a) In the short product information and user instructions, it is stated that the product is still insufficient in certain aspects, the validity period of the marketing authorization is one year and the marketing authorization will be re-evaluated annually.

b) The marketing authorization holder must apply for marketing authorization renewal at least ninety days before the end of the marketing authorization validity period, together with an interim report on the status of specific obligations to which it is subject.

c) If the marketing authorization renewal application is made within the period specified in subparagraph (b), the product may remain on the market until the Agency notifies its decision.

ç) When requested by the Agency, the marketing authorization holder must submit a periodic benefit/risk assessment report to the Agency immediately or at least once every six months.

(2) The Agency concludes the marketing authorization renewal application within the scope of subparagraph (b) of the first paragraph within ninety days.

Specific obligations for a conditional marketing authorisation (emergency use authorization)

ARTICLE 35 – (1) The specific obligations specific to the medicinal product for human use for which a conditional authorization application is made are determined by the Agency.

(2) After determining the specific obligations, it is obligatory for the marketing authorization holder to complete the ongoing studies or carry out new studies for conditionally authorized products in order to ensure that the requirements specified in the second paragraph of Article 33 are met and that the benefit/risk balance is positive. Specific requirements may also be imposed for the collection of pharmacovigilance data in addition.

(3) The Agency publishes the specific requirements of the conditionally authorized product and the calendar required for the completion of these obligations on the official website of the Agency.

(4) In case all specific requirements are fulfilled, a marketing authorization is not subject to specific requirements is issued by the Agency.

Application for exceptional authorization, evaluation of the application and validity of the marketing authorization

ARTICLE 36 – (1) In the exceptional cases listed below, an application for an exceptional marketing authorization may be made, provided that certain conditions, especially regarding the safety of the medicinal product for human use, are fulfilled by the applicant:

a) The therapeutic indications of the medicinal product for human use are so rare that it cannot be expected from the applicant to provide comprehensive evidence, or

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

c) Collecting such information goes against generally accepted medical ethics.

(2) An exceptional authorization can only be granted if the applicant proves for objective, verifiable reasons that he cannot provide comprehensive data on the efficacy and safety of the medicinal product under normal conditions of use, and it meets the requirements set out in Annex-1.

(3) The validity of the marketing authorization depends on the annual re-evaluation of these conditions.

Compulsory license

ARTICLE 37 – (1) For products approved by the President of the Republic to be produced under a compulsory marketing authorization within the scope of Article 132 of the Industrial Property Law, a marketing authorization application can be made to the Agency within the scope of the requirements, the detailed aspects of which are determined by the Agency.

Pricing

ARTICLE 38 – (1) The Agency may apply a fee for the activities within the scope of this Regulation.

CHAPTER FIVE
Miscellaneous and Final Provisions

Guideline

ARTICLE 39 – (1) The Agency publishes guidelines or communiques for the implementation of this Regulation when it deems necessary.

Confidentiality

ARTICLE 40 – (1) Information submitted to the Agency by the applicant to obtain a marketing authorization for a medicinal product for human use is confidential. This confidentiality is protected by the Agency.

Withdrawal

ARTICLE 41 – (1) The provisions of the Withdrawal Regulation published in the Official Gazette dated 19/11/2015 and numbered 29537 shall be applied for the recall and withdrawal procedures for the products that are subject to withdrawal from the products within the scope of this Regulation.

Repealed regulations

ARTICLE 42 – (1) Regulation on the Marketing Authorization of Medicinal Products for Human Use published in the Official Gazette dated 19/1/2005 and numbered 25705 and Regulation for the Evaluation of Bioavailability and Bioequivalence of Pharmaceutical Products published in the Official Gazette dated 27/5/1994 and numbered 21942 have been repealed.

References

ARTICLE 43 – (1) References made to Marketing Authorization of Medicinal Products for Human Use, which was repealed with Article 42, shall be deemed to have been made to this Regulation.

Compliance with European Union legislation

ARTICLE 44 – (1) This Regulation has been prepared within the framework of harmonization with the European Union legislation taking into account the Directive of the European Parliament and of the Council on Medicinal Products for Human Use dated 6/11/2001 and numbered 2001/83/EC and the Commission Regulation on Conditional Marketing Authorisation for Medicinal Products for Human Use dated 29/3/2006 and numbered 507/2006/EC.

Products with permission and registration certificate

PROVISIONAL ARTICLE 1 – (1) Pursuant to the temporary 1st and 2nd provisional articles of the Traditional Herbal Medicinal Products Regulation published in the Official Gazette dated 6/10/2010 and numbered 27721, It is obligatory to complete the licensing process within one year from the effective date of this Regulation for products that have an intermediate product permit or for which a marketing authorization application is made while the process for the intermediate product permit is in progress, and it has been decided to be considered within the scope of medicinal product for human use and the registration process is still in progress. The permit certificate of the products with a permit certificate of intermediate product that does not obtain a marketing authorization during this period are canceled and their marketing authorization applications are returned. The production, import and placing on the market of these products, whose intermediate product permit certificates have been revoked, are not allowed. Commercially available products can be found in the market until the end of their shelf life. Marketing authorization applications for products that do not have a marketing authorization and whose authorization process is not completed within one year from the effective date of this Regulation are also returned.

(2) For the following products, it is obligatory to complete the authorization process within one year from the effective date of this Regulation. Import permits, permits and registration documents of products that cannot obtain a marketing authorization during this period will be invalid:

a) Radionuclide generators, kits, radionuclide precursor radiopharmaceuticals and industrially prepared radiopharmaceuticals, which are placed on the market with a registration document and for which a marketing authorization application has been made.

b) Human blood products and immunological medicinal products for human use placed on the market with an import permit and for which a marketing authorization application has been made.

Transition to certified marketing authorization

PROVISIONAL ARTICLE 2 – (1) For medicinal products for human use that do not have a certified marketing authorization, an application for certified marketing authorization is made to the Agency within sixty months from the date of entry into force of this Regulation, in line with the transition calendar announced by the Agency. In this context, a lost marketing authorization application is made for medicinal products for human use for which the original marketing authorization cannot be submitted.

(2) Variation applications made to the Agency for medicinal products for human use, for which an application for transition to a certified marketing authorization is not made within the calendar period specified in the first paragraph, shall not be processed.

(3) It is not obligatory to apply for a certified marketing authorization for medicinal products for human use whose marketing authorization has been suspended. Before a medicinal product for human use, whose marketing authorization has been suspended and which does not have a certified marketing authorisation, is placed on the market, it is necessary to obtain a certified marketing authorization for the product in question.

Application for transition to marketing authorization of an immunological medicinal product for human use

PROVISIONAL ARTICLE 3 – (1) Within one year from the effective date of this Regulation, an application for an immunological human medicinal product registration is made to the Agency for medicinal products for human use, currently authorized as blood products, based on blood components whose active substance(s) are not derived from human blood or plasma, but which include blood components derived from human blood or plasma in the production process. For these applications, it is obligatory to complete the marketing authorization change process within one year from the date of application. For medicinal products for human use for which the marketing authorization change process is not completed within this period, the marketing authorization suspension procedure is applied in accordance with subparagraph (h) of the first paragraph of Article 22.

Analysis of permit for human blood products to be placed on the market

PROVISIONAL ARTICLE 4 – (1) Until the first paragraph of article 29 enters into force, analyzes determined by the Agency according to the product for each batch of medicinal product for human use must be done in the Agency's laboratory or in a laboratory accepted by the Agency for this purpose.

Co-marketed medicinal products for human use

PROVISIONAL ARTICLE 5 – (1) Only for medicinal products for human use, for which a co-marketing authorization application has been made by submitting Module 1 prepared in accordance with Annex-1 and the registration process is still in progress before the publication date of this Regulation, If the marketing authorization holders want to make the application files a full and complete file, they submit all the necessary modules to the Agency within thirty days from the publication of the Regulation.

(2) For medicinal products for human use subject to co-marketing that were authorized by submitting Module 1 prepared only in accordance with Annex-1 before the publication date of this Regulation, in case the marketing authorization holders want to make the marketing authorization files full and complete, they submit all the necessary modules to the Agency within six months after the publication of the Regulation.

Enforcement

ARTICLE 45 – (1) This Regulation shall enter into force

a) one year after the publication for sub-paragraphs (i) and (j) of the first paragraph of Article 22,

b) on 1/1/2025 for first paragraph of Article 29,

c) on the date of publication for other provisions,

Execution

ARTICLE 46 – (1) The provisions of this Regulation shall be executed by the President of the Turkish Medicines and Medical Devices Agency.

Click for annex.