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,

ı) **(Appended:OG-24/09/2022-31963)** Medical teas,

i) **(Appended:OG-24/09/2022-31963)** Medicinal products used in aromatherapy.

(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) **(Amended phrase:OG-28/09/2022-31963)** Medicinal product for human use (medicine) 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) **(Amended:OG-28/09/2022-31963)** Co-marketed product: A medicinal product for human use that has the same qualitative and quantitative composition, the same pharmaceutical

form, the same manufacturing site(s) and is exactly the same in all respects except for the trade name, with an authorized medicinal product for human use,

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) **(Amended:OG-28/09/2022-31963)** Reference medicinal product: a medicinal product for human use permitted or authorised by the Agency, ICH (International Council for Harmonization) founding or permanent member competent authorities, Therapeutic Goods Administration of Australia (TGA) or Medicines and Healthcare products Regulatory Agency of England (MHRA) with a full dossier, together with administrative, quality, (**Amended phrase**: **OG-27/5/2023-32203)** nonclinical and clinical data, in terms of active substance (s) proven to have scientifically acceptable efficacy, quality and safety,

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) **(Repealed:OG-24/09/2022-31963)**

(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) **(Amended:OG-24/09/2022-31963)** In case the clinical studies are carried out in Türkiye; information or document indicating that the said clinical studies have been given trial permission by the Agency if it is carried out outside Türkiye;

1) Applicant's declaration including the statement that it meets the scientific and ethical requirements set out in the Regulation on Clinical Research of Medicines and Biological Products.

2) For clinical studies authorized by the Agency, competent authorities of the Therapeutic Goods Administration of Australia (TGA) or Medicines and Healthcare products Regulatory

Agency of England (MHRA), ICH (International Council for Harmonization) founding or permanent member competent authorities, information or document indicating that the said clinical studies have been granted trial authorization by the Agency, the Therapeutic Goods Administration of Australia (TGA) or Medicines and Healthcare products Regulatory Agency of England (MHRA), ICH (International Council for Harmonization) founding or permanent member competent authorities.

3) For clinical studies authorized by other health authorities other than the Agency, the Therapeutic Goods Administration of Australia (TGA) or Medicines and Healthcare products Regulatory Agency of England (MHRA), ICH (International Council for Harmonization) founding or permanent member competent authorities, (GCP) inspection report conducted by the Agency, the Therapeutic Goods Administration of Australia (TGA) or Medicines and Healthcare products Regulatory Agency of England (MHRA), ICH (International Council for Harmonization) founding or permanent member competent authorities in line with the relevant guideline requirements and demonstrating that the said studies are appropriate

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) **(Amended:OG-24/09/2022-31963)** In applications for co-marketed human medicinal products, Commitment stating that medicinal products for human use subject to co-marketing are exactly the same, that all variation applications will be made in accordance with the relevant guideline and that they will be manufactured at the same manufacturing site(s).

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) (**Amended**: **OG-27/5/2023-32203)** A document issued to these places by a competent health authority showing that the active substance(s) and, where applicable, the intermediate(s) used in the manufacturing process of the active substance 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.

3) (**Appended**: **OG-27/5/2023-32203)** In cases where the documents specified in the first sub-clause cannot be submitted for the intermediate manufacturing site(s) used in the manufacturing process of the active substance, a declaration that the manufacturing is carried out in accordance with good manufacturing practices regulated based on the inspection carried out by the active substance manufacturer and, if requested by the Agency, an inspection report.

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, **(Amended phrase:OG-24/9/2022-31963)** 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, , **(Amended phrase:OG-24/9/2022-31963)** 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

possessing the same qualitative and quantitative composition in terms of active substance(s) and 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 **(Amended phrase:OG-24/9/2022-31963)** 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 **(Amended phrase:OG-24/9/2022-31963)** 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 **(Amended phrase:OG-24/9/2022-31963)** 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, **(Amended phrase:OG-24/9/2022-31963)** 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) **(Amended phrase:OG-24/9/2022-31963)** 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.

ç) **(Appended: OG-27/5/2023-32203)** Failure to submit the necessary information and documents to the Agency at the end of the period specified in accordance with the second paragraph.

(2) **(Appended: OG-27/5/2023-32203)** The date information submitted for the information and documents to be submitted to the Agency in accordance with subparagraph (c) of this paragraph shall be deemed appropriate by the Agency in terms of current scientific requirements and shall not exceed three years. The Agency may apply an exception to this issue for conditional marketing authorization applications made within the scope of Article 33.

(3) **(Appended: OG-27/5/2023-32203)** In the event that a re-authorization application is made for medicinal products for human use whose application is rejected within the scope of subparagraph (c) of the first paragraph, in case of priority decisions in the marketing authorization and/or inspection processes, if any, given by the Priority Assessment Committee for the said products and for the analysis made by the Department of Analysis and Control Laboratories or by the Turkish Energy, Nuclear and Mineral Research Agency for radiopharmaceutical products if the analysis reports issued for the finalized and ongoing analyzes are deemed appropriate, the marketing authorization processes of the relevant products shall be directly initiated.

(4) **(Appended: OG-27/5/2023-32203)** In the event that a re-authorization application is made for medicinal products for human use whose application is rejected due to the procedure within the scope of subparagraph (c) of the first paragraph, the commitment that the current dossier and changes approved by the Agency are reflected shall be submitted in the file."

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) **(Amended:OG-24/09/2022-31963)** The marketing authorization period, which is two hundred and ten days for medicinal products for human use for which a marketing authorization application is made in accordance with Article 37/A, shall be ninety days.

(4) **(Appended:OG-24/09/2022-31963)** In cases where additional information and documents are requested from the applicant within the scope of Articles 8, 9, 10, 33, 36 and 37/A when necessary during the marketing authorization granting process by the Agency, the marketing authorization granting period shall be suspended until the relevant information and documents are provided.

Prioritization in marketing authorization processes

ARTICLE 15 – (1) **(Amended: OG-27/5/2023-32203)** Marketing authorization procedures shall be carried out over electronic systems according to the starting date of the marketing authorization process. However, applications approved by the Agency's Priority Assessment Committee among the products applied according to Article 8, 9, 33, 36 or 37/A shall be evaluated as a priority in the marketing authorization procedures.

(2) **(Amended: OG-27/5/2023-32203)** The marketing authorisation granting procedures of such products shall be completed within the periods specified in the relevant guidelines published by the Agency.

(3) **(Amended:OG-24/09/2022-31963)** The provisions in the first and fourth paragraphs of Article 14 regarding the suspension of the period shall also apply to 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 **(Amended phrase:OG-24/09/2022-31963)** cannot be proved or

d) **(Appended:OG-24/09/2022-31963)** the non-compliance of the qualitative and quantitative formula and the data on the quality of the product.

(3) **(Appended:OG-24/09/2022-31963)** Information on the assessment of marketing authorization applications rejected under this article shall not be published.

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

ARTICLE 19 – (Amended:OG-24/09/2022-31963) (1) In case of rejection of the marketing authorization application on the fundamental grounds, the decision shall be notified to the applicant with justification or in case of failure to notify, it may be announced on the website of the Agency. The applicant shall hold the right to submit to the Agency a written objection to the decision within forty-five days from the date of notification or announcement. In case 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 published in the Official Gazette 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) **(Amended:OG-24/09/2022-31963)** With the exception of only aroma difference in lozenges, oral sprays, chewable tablets, fish oil preparations, nicotine gums and pediatric vitamin syrups, primary packaging forms of human medicinal products and large volume parenterals in bottle and bag form with only single-dose multi-dose usage difference and besides these extension applications within the scope of the Regulation on Variations in Authorized Medicinal Products for Human Use published in the Official Gazette dated 18/12/2021 and numbered 31693; 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 authorized by the Agency and 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 medicinal products for human use that are scientifically and technologically proven to be superior to an authorized medicinal product for human use or that have a justification approved by the Agency shall be assessed separately. In the assessment 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 shall be 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) **(Amended:OG-24/09/2022-31963)** A medicinal product for human use cannot be granted a marketing authorization with the same name as a traditional herbal medicinal product, medical device or homeopathic medicinal product."

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

(6) **(Amended:OG-24/09/2022-31963)** The list of medicinal products for human use authorized by the Agency shall be announced at least once a month on the official website of the Agency under the name of List of Authorized Medicinal Products for Human Use and once a year in the Official Gazette.

(7) **(Appended:OG-24/09/2022-31963)** The Agency may issue a publicly available assessment report that does not contain commercially confidential information regarding the pharmaceutical and pre-clinical tests, clinical trials, risk management system and pharmacovigilance system of the relevant medicinal product for human use. This assessment report shall be updated when new information is obtained that is important for the assessment of the quality, safety or efficacy of the relevant medicinal product for human use. The public assessment report shall contain a summary, in particular a section on the conditions of use of the medicinal product for human use.

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) **(Amended phrase: OG-14/12/2022-32043)** In the event that the nonconformity of at least one of the situations is detected and confirmed, the marketing authorization of the medicinal product for human use shall be suspended by the Agency according to the result of the evaluation made by the Agency, which will include the safety of the relevant nonconformity, or if the cancellation of marketing authorization of the product is requested by the marketing authorization holder.

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) **(Amended:OG-24/09/2022-31963)** Failure to fulfill the obligations in the first and second paragraphs of Article 25,

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

o) **(Amended:OG-24/09/2022-31963)** Failure of the marketing authorization holder to place the medicinal product for human use which is important for the sustainability of public health and access to the medicine on the market within six months from the date of the request, despite the request by the Agency.

ö) (**Appended**: **OG-27/5/2023-32203**) In the marketing authorization transfer applications made within the scope of Article 26, failure of the marketing authorization holder to submit the certificate showing that the manufacturing site(s) subject to the marketing authorization manufacture in accordance with the good manufacturing practice guidelines and the Manufacturing Site Permit Certificate for the active substance manufacturing site(s) operating in Türkiye.

(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 – (Amended:OG-24/09/2022-31963) (1) In the presence of one of the following conditions, the marketing authorization granted for the medicinal product for human use shall be cancelled:

a) **(Amended: OG-27/5/2023-32203)** For products whose marketing authorization has been suspended due to one or more of the situations listed in the first paragraph of Article 22, the documents proving the contrary of the reason for suspension are not submitted within six months at the latest from the date of suspension of the marketing authorization by the marketing

authorization holder or the documents explaining the situation are not found appropriate 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) Failure to supply the products to 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 complete and full 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 shall also be revoked. However, the marketing authorization status of the product(s) for which a co-marketing authorization is issued with a full and complete file shall be updated if an application is made to the Agency in accordance with the relevant guideline.

(3) In case applicants request the cancellation of existing marketing authorizations in case of extension applications made within the scope of the Regulation on Variations in Authorized Medicinal Products for Human Use, the existing marketing authorizations shall be cancelled without simultaneous suspension when the marketing authorisation is issued for the products for which the extension application is made.

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

(5) Marketing authorization whose cancellation process is deemed appropriate and suspended according to subparagraph (b) of the first paragraph shall be announced on the official website of the Agency for a period of six months. Marketing authorization in this situation shall be 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 shall not continue.

(6) 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 co-marketed and the marketing authorization application is made with a complete and full dossier, it shall be obligatory for the marketing authorization holder to submit the list of other medicinal product(s) for human use subject to co-marketing to the Agency.

(7) **(Amended: OG-27/5/2023-32203)** Pursuant to subparagraphs (i), (j), (o) and (ö) of the first paragraph of Article 22, the marketing authorization suspension period of the suspended products may be extended for another six months if deemed appropriate by the Agency.

(8) **(Amended: OG-27/5/2023-32203)** For medicinal products for human use, which are included in the list of medicines supplied from abroad or which may pose a public health risk due to their inability to be supplied, the Agency may extend the marketing authorisation suspension period regarding the matters within the scope of the fifth and seventh paragraphs.

(9) The list of medicinal products for human use whose marketing authorization has been cancelled by the Agency shall be announced on the official website of the Agency.

(10) **(Appended: OG-27/5/2023-32203)** For a medicinal product for human use conditionally authorized within the scope of Article 34, in the event that the Authority decides to cancel the conditional marketing authorization as a result of the annual assessment the

marketing authorization cancellation procedures of the said products shall be carried out in accordance with Article 22, without the marketing authorization suspension process."

Loss of marketing authorization certificate or product dossier by the holder

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

(2) In case the marketing authorization dossier 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 dossier is made to the Agency by the applicant or the marketing authorization holder. A copy of the dossier 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) **(Amended: OG-27/5/2023-32203)** Due to the quality or efficacy or safety of the medicinal products for human use imported, exported or manufactured in Türkiye under license; suspension or cancellation of the marketing authorization or withdrawal or recall from the market in other countries where it is authorized; rejection of the marketing authorization application in other countries where the marketing authorization application is made or notification of the withdrawal of the application by the applicant to the Agency.

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

(3) **(Amended:OG-14/12/2022-32043)** The marketing authorization holder or the applicant is obliged to make an application in accordance with the principles set forth in this Regulation, to fulfill the commitments made to the Agency and to confirm the accuracy of the information and documents submitted to the Agency, and accept 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.

(6) **(Appended:OG-24/09/2022-31963)** The Agency may also request additional information and documents for products for which the marketing authorization has been issued in accordance with the current scientific requirements. The marketing authorization holder shall be obliged to submit the information and documents requested by the Agency to the Agency within the specified period.

(7) **(Appended:OG-24/09/2022-31963)** Marketing authorization holders shall be obliged to make records of the products in accordance with the requirements determined by the Agency in the information management system of the Agency and to ensure that these data are up-to-date

Transfer of marketing authorization

ARTICLE 26 – (1) The marketing authorization 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) **(Amended:OG-24/09/2022-31963)** The court decision from the court stating that the marketing authorisation has been transferred by the court, the decision of the enforcement office regarding the sale of the marketing authorisation through forced execution, or the contract drawn up in the presence of a notary public and containing the following issues;

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

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

3) A report stating that the current medicinal product for human use dossier 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) **(Amended: OG-27/5/2023-32203)** Name, surname, address, telephone number and KEP address of the person who has taken over the marketing authorization, updated summary of product characteristics of the medicinal product for human use, package leaflet, a copy of the inner and outer packaging, and for the transfers made through a notary public, the original

of the previous marketing authorization for the product in question; where updated summary of product characteristics and package leaflet cannot be provided, a fully prepared commitment by the transferee, stating that all necessary changes and updates regarding the summary of product characteristics and package leaflet of the medicinal product for human use will be made in line with the relevant guidelines, certificate showing that the manufacturing site(s) based on the marketing authorization manufactures in accordance with the good manufacturing practices guidelines and the Production Site Permit Certificate for the active substance manufacturing site(s) in Türkiye.

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) **(Amended:OG-24/09/2022-31963)** In case the applicant is not a manufacturer of medicinal products for human use to be manufactured in Türkiye, the contract for contract manufacturing with a manufacturer that meets the conditions set forth in the Regulation on Manufacturing Plants of Medicinal Products for Human Use and the registration certificate of the parties.

(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) **(Amended: OG-27/5/2023-32203)** In accordance with the relevant guideline published by the Agency, with the exception of the cases deemed necessary by the Agency, if a letter of commitment prepared by the transferee company stating that all necessary changes and updates will be made in relation to the medicinal product for human use after the transfer process takes place, the necessary updates regarding the existing product dossier and the procedures for eliminating the deficiencies, if any, shall be made in accordance with the relevant guidelines after the marketing authorization transfer procedures of the medicinal product for human use are made and the sales permit cannot be applied for without approval. However, when deemed necessary by the Agency, an application may be requested for updates to the existing product dossier and, if any, for actions to eliminate deficiencies.

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.

(5) **(Appended:OG-24/09/2022-31963)** Failure to submit the information and documents requested by the Agency or the date on which they will be submitted and the necessary explanation regarding the failure to submit such information and documents, the transfer application shall be cancelled.

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) **(Amended:OG-24/09/2022-31963)** For medicinal products for human use to be marketed for the first time through obtaining marketing authorisation from the Agency the marketing authorization holder shall submit to the Agency the document issued by the Agency in case of performing storage activities in the facilities belonging to its own private or legal entity for medicinal products for human use for which sale price application is approved by the Agency and in other cases, the document issued by the Agency for the storage place, the document signed between the parties for the storage of the product and the registration certificate of the parties together with the application for sale permit.

(3) **(Amended:OG-24/09/2022-31963)** The Agency shall examine the mock-up and the package leaflet of the medicinal product for human use for which the sales permit is applied for and whose price is approved by the Agency in terms of the necessary information.

(4) **(Amended:OG-24/09/2022-31963)** It shall not necessary to re-obtain a sales permit for transactions that cause changes in the labelling or characteristics of the medicinal product for human use, or the package leaflet as per the marketing authorisation. However, after the transfer of the manufacturing site from abroad to Türkiye or from Türkiye to abroad,seasonal, pre-pandemic or pandemic influenza vaccine strain/strains are replaced with a new one, packaging size change, marketing authorization transfer procedures or for the products whose marketing authorization suspension status revoked in accordance with the fifth paragraph of Article 22 before placing on the market a sales permit must be obtained by applying to the Agency without the documents specified in the second paragraph.

(5) **(Appended:OG-24/09/2022-31963)** For medicinal products for human use to be used in emergencies against public health threats recognized by the World Health Organization or the European Union or accepted by the Ministry of Health and to be supplied only by the public, the Agency may define restrictions in the sales permit for public health institutions and organizations that provide services in which the products in question may be placed on the market. These restrictions shall be specified in the sales permit.

Permit of human blood products to be placed on the market

ARTICLE 29 – (Amended:OG-24/09/2022-31963) (1) For blood products that have a sales permit, have a permit but have been applied for or have a marketing authorization, the marketing authorization holder shall apply to the Agency to obtain a marketing authorization for each batch of the product in accordance with the guideline published by the Agency in addition to the matters specified in Article 28 before placing the product on the market.

(2) **(Amended: OG-27/5/2023-32203)** I In cases where blood products or human medicinal products containing blood products and blood products are included to be active substance or excipient in the content of the human medicinal product, the analyzes determined according to the product for each batch of products should have been conducted in the Agency's laboratory or in a laboratory accepted by the Agency for this purpose.

(3) **(Amended:OG-24/09/2022-31963)** 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 shall be submitted to the Agency and the analyzes conducted in accordance with the second paragraph and the aforementioned documents are deemed appropriate by the Agency, the relevant medicinal products for human use shall be granted permit to be placed on the market:

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

b) In cases where each batch of bulk blood product or each batch of finished blood product or blood product is not included as an active substance in the content of the human medicinal product, for each batch of blood product which is excipient batch/lot release certificate approved by the Health Authority deemed appropriate by the Agency (apostille annotated/consular approved if the document is obtained from abroad), in case of failure to submit the batch/lot release certificate the documents specified in the guideline published by the Agency,

c) Certified analysis certificate for each batch of bulk or finished product,

ç) A document, issued by the marketing authorization holder and, where applicable, by the licensor or the manufacturer, showing in which country/countries each batch was sold, with quantities and document declaring the status of unsold products for cases where they have not been sold yet, in cases where the batches is only imported to Türkiye, document showing the countries/countries where each batches of plasma pools used in the relevant batches is used, and the quantities in which other products are sold,

d) **(Amended: OG-27/5/2023-32203)** The rules based on plasma donation issued by the licensor or manufacturer, the date of collection of the plasma and the type of donor (volunteer, paid) and the commitment that the list of donors or donor centers will be submitted when deemed necessary by the Agency,

e) Documents prepared in accordance with the guidelines published by the Agency and showing that HBsAg, HIV 1/2 and HCV RNA tests are applied and results for samples belonging to each plasma pool,

f) **(Amended: OG-27/5/2023-32203)** Document issued by the manufacturer or licensor company stating that the donors are safe in terms of diseases or suspicion of diseases determined by the Agency (such as Creutzfeld-Jacob (CJ) disease) and that there are no donors with these diseases among the donors for each batch, final bulk or finished product and each batch of

excipient(s) that are blood products in cases where the blood product is not present as an active substance in the content of the human medicinal product,

g) Up-to-date variation commitment of the product whose batch number is specified and issued by the marketing authorization holder and, where applicable, the licensor or manufacturing company."

(4) **(Amended: OG-27/5/2023-32203)** In the case of medicinal products for human use, which are intended to be imported as bulk products of blood products and placed on the market by producing the finished product in Türkiye, 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/manufactured 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 manufactured in Türkiye and authorized and obtained sales permit in this direction, and provided that the analyzes made in accordance with the second paragraph and the relevant information and documents are found appropriate, if the commitment stated in only subparagraph (g) of the third paragraph is submitted, the permit for placing on the market is granted.

(5) **(Appended:OG-24/09/2022-31963)** Where the blood product is found as an excipient in addition to the active substance in the human medicinal product, the information documents in paragraphs (b), (c), (e) and (f) of the third paragraph must be submitted to the Agency in addition to the documents requested for each batch of the excipient(s) that are blood products."

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) **(Amended:OG-24/09/2022-31963)** The following documents and information shall be submitted to the Agency by notifying the amount requested to be placed on the market in order to obtain a marketing authorization for immunological medicinal products for human use for which a marketing authorization application has been submitted or authorization has been granted:

a) Batch/lot release certificate approved by the Health Authority deemed appropriate by the Agency for each batch or finished product (apostille annotated/consular approved if the document is obtained from abroad), in case the batch release certificate cannot be submitted, the documents specified in the guideline published by the Agency,

b) Certified analysis certificate for each batch of bulk or finished product,

c) The current variation commitment for the product to be imported and whose batch number is specified, issued by the marketing authorization holder and, where applicable, by the licensor or the manufacturer,

(4) **(Amended:OG-24/09/2022-31963)** In cases where it deems necessary, the Agency may request that all or part of the analyzes included in the batch/lot release certificate specified in subparagraph (a) of the third paragraph be performed by the Agency's laboratory."

(5) **(Appended:OG-24/09/2022-31963)** In case of conformity of the documents submitted within the scope of the application for immunological medicinal products which has permit and for which marketing authorization has been applied for and the results of the analysis of the products for which marketing authorization has been applied for, the relevant batch shall be permitted to be placed on the market.

(6) **(Amended: OG-27/5/2023-32203)** Except for the allergen products specified in the relevant guideline for the authorized allergen products with a sales permit; the marketing authorization holder shall apply to the Agency with the information and documents specified in the guideline published by the Agency to obtain the permit for placing on the market for each batch of the product before placing the product on the market. For authorized allergen products, if the documents submitted within the scope of the application are appropriate, the relevant batch is allowed to be placed on the market.

(7) **(Appended:OG-24/09/2022-31963)** The analyses determined by the Agency for each batch of human medicinal products based on blood components that are not obtained from human blood or plasma but that are obtained from human blood or plasma in the manufacturing process must have been carried out in the Agency's laboratory or in a laboratory accepted by the Agency for this purpose. Applications shall be submitted for the products in question with the information and documents specified in the guideline published by the Agency.

(8) **(Appended:OG-24/09/2022-31963)** Applications shall be made with the information and documents specified in the guideline published by the Agency for the permission of placing on the market of each batch of finished product of vaccines and immune sera that are authorized or conditionally authorized (Emergency Use Authorization) to be filled and/or manufactured in Türkiye."

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, Compulsory License, Reliance

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.

Reliance

ARTICLE 37/A- (1) **(Appended:OG-24/09/2022-31963)** Previous assessment made by other medicine authorities or regional or international organizations with comparable standards may be taken into account in accordance with the guidelines published 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) **(Amended:OG-24/09/2022-31963)** Pursuant to the 1st and 2nd provisional articles of the Regulation on Traditional Herbal Medicinal Products published in the Official Gazette dated 6/10/2010 and numbered 27721, it shall be obligatory to complete the marketing authorization process within two years from the date of entry into force of this Regulation for products that have an intermediate product permit or for which 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 marketing authorization process is still in progress. During this period, the permit certificates of the products with intermediate product permit certificate that cannot obtain a marketing authorization shall be cancelled and their marketing authorization applications shall be returned. These products, whose intermediate product permit certificates have been cancelled, shall not be permitted to be manufactured, imported and placed on the market. Commercially available products can be available in the market until the end of their shelf life. For products whose marketing authorization transaction are not completed within two years from the date of entry into force of this Regulation and do not have a permit certificate marketing authorization applications shall also be returned."

(2) For the following products, **(Amended: OG-14/12/2022-32043)** it is obligatory to complete the authorization process until 31/12/2023. 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 or blood product or blood product

PROVISIONAL ARTICLE 3 – (Amended with title:OG-24/09/2022-31963) (1) For medicinal products for human use that are not derived from human blood or plasma but are currently authorized as blood products based on blood components obtained from human blood or plasma in the manufacturing process, an immunological human medicinal product marketing authorization application shall be made to the Agency within two years from the date of entry into force of this Regulation. For these applications, it shall be 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 shall be 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 – (Repealed:OG-24/09/2022-31963)

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.

PROVISIONAL ARTICLE 6 – (1) **(Appended:OG-24/09/2022-31963)** Allergen products manufactured in any of the countries of the European Union and currently on the market in the member countries of the European Union may be placed on the market until 31/12/2024, provided that the following requirements are met:

a) Temporary permit application is made with Module 1 prepared in accordance with Annex-1.

b) Annex 6.15 of the application form in Module 1 contains only the current Pharmaceutical Product Certificate showing that the product in question is available on the market of the relevant country.

c) During the preliminary assessment, the Agency shall examine the application for allergenic product temporary permit made with Module 1 and officially notifies the applicant that the application has been accepted or rejected. Notification that the application has been accepted shall be considered as the start date of the temporary permit assessment process. Temporary permit assessment process shall be finalized within thirty days at the latest. The time elapsed for the assessments of external organizations; the time elapsed for official holidays

and the time elapsed for extraordinary situations except for weekend holidays shall not not included in the temporary permit period.

ç) The SPC, PL and labelling of the product shall include the date of the temporary permit, the temporary permit number and the information of the temporary permit holder until the marketing authorization process is completed.

d) In order to place the temporarily authorized products on the market, the Authority shall be applied in accordance with the requirements of Article 28 and the relevant guideline.

e) The marketing authorization applications made by submitting all modules in accordance with the 6th and 8th articles of the temporarily permitted products shall be assessed in accordance with the 12th article and, if deemed appropriate, the scientific and administrative assessment process is initiated. If the said process is deemed appropriate, the product shall be granted marketing authorization. For marketing authorization applications made with Module 1, all modules shall be submitted and the product shall be authorized if the application is completed and the scientific and administrative assessment is approved by the Agency. In order for the products to be placed on the market with the information based on the marketing authorization for the authorized products, an application for a sales permit shall be made to the Agency in accordance with the requirements of Article 28.

f) The application must be completed with all modules by 31/12/2024 and the products in question must be authorized. During this period, the temporary permission of the products whose marketing authorization process has not been completed or the marketing authorization application has been rejected due to the procedural or fundamental basis shall be canceled and their placing on the market shall be suspended. Temporary permit applications to be made again for the products whose application is rejected within the scope of this paragraph shall not be taken into consideration by the Agency.

g) In the event that the application is rejected in accordance with the provisions of Article 18 in the scientific assessment process of the products that are temporarily permitted and the marketing authorization process is ongoing, the temporary permit shall be canceled and the supply to the market shall be suspended and the products on the market shall be withdrawn from the market in accordance with the relevant provisions of the Recall Regulation.

Generic medicinal product and hybrid applications

PROVISIONAL ARTICLE 7- (1) **(Appended:OG-24/09/2022-31963)** Generic medicinal products authorized in Türkiye can be used as reference medicinal products in the generic medicinal product and hybrid product marketing authorization applications to be made until 31/12/2022.

Medical devices for which the opinion of the notified body or CE certificate is requested

PROVISIONAL ARTICLE 8- (1) **(Appended:OG-24/09/2022-31963)** For medicinal products for human use containing an integrated medical device for which marketing authorization has been applied for or authorized in accordance with this Regulation, it shall be obligatory to submit an notified body opinion or CE certificate as specified in Annex-1 until **(Amended phrase: OG-27/5/2023-32203)** 31/12/2028 and marketing authorization applications made until the said date shall be made in accordance with the provisions of the relevant guideline.

Procedural rejection of the application

PROVISIONAL ARTICLE 9- (1) **(Appended:OG-24/09/2022-31963)** Subparagraph (c) of the first paragraph of Article 13 shall not be applied until 1/1/2023.

Acceptance of clinical trials

PROVISIONAL ARTICLE 10- (1) **(Appended:OG-24/09/2022-31963)** Sub-clauses (2) and (3) of sub-paragraph (m) of the first paragraph of Article 8 shall not be applied until **(Amended phrase: OG-27/5/2023-32203)** 1/1/2025.

Reference medicinal product description

PROVISIONAL ARTICLE 11- (1) **(Appended:OG-24/09/2022-31963)** With the exception of biosimilar and bioavailability studies, subparagraph (çç) of the first paragraph of Article 4 shall not be applied until 1/1/2024. A human medicinal product that has been scientifically proven to have acceptable efficacy, quality and safety by the date in question and has been permitted or authorized to be placed on the market for the first time in the world in terms of active substance (s) shall be considered as the reference medicinal product.

Medicinal products for human use not included in the list of authorised medicinal products for human use

PROVISIONAL ARTICLE 12- (1) **(Appended:OG-24/09/2022-31963)** In accordance with this Regulation, for products not included in the list of authorized medicinal products for human use announced on the official website of the Agency, the marketing authorization holders shall apply to the Agency until 31/12/2022 with the documents determined by the Agency. Products whose applications are approved shall be added to the list. The marketing authorizations of the products that are not deemed appropriate to be added to the list or that are not applied according to the requirements determined by the Agency until 31/12/2022 shall be considered invalid."

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) **(Repealed:OG-24/09/2022-31963)**

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.

Annex-1

PARTICULARS AND DOCUMENTS TO BE SUBMITTED AT THE MARKETING AUTHORIZATION APPLICATION FOR MEDICINAL PRODUCTS FOR HUMAN USE

Introduction and general principles

The particulars and documents accompanying an application for marketing authorization pursuant to the provisions of this Regulation, shall be presented to the Agency in accordance with the requirements set out in this Annex. While preparing the application dossier, the Common Technical Document (CTD) Guideline published by the Agency shall be followed.

(2) The particulars and documents shall be presented as five modules:

Module 1 Administrative Data

Module 2 Quality Information, **(Amended phrase:OG-24/9/2022-31963)** Nonclinical and Clinical Summaries,

Module 3 Chemical, Pharmaceutical and Biological Information,

Module 4 **(Amended phrase:OG-24/9/2022-31963)** Nonclinical Reports,

Module 5 Clinical Study Reports.

These five Modules shall be presented in full compliance with the format, content and numbering system detailed in the CTD Guideline published by the Agency.

(3) Submission of the CTD to the Agency is applicable irrespective of whether it is a full or abbreviated application for all type of marketing authorisation applications, and it is also applicable for all types of products including new chemical entities, radiopharmaceuticals, human medicinal products obtained from human blood or plasma, vaccines and herbal medicinal products.

(4) In assembling the dossier for application for marketing authorization, applicants shall also take into account the scientific guidelines on quality, safety and efficacy and other legislation published by the Agency, pertaining to medicinal products for human use.

(5) With respect to the quality part (chemical, pharmaceutical and biological) of the dossier, all monographs including general monographs and general chapters are applicable.

(6) The manufacturing process shall comply with the requirements of the Regulation on the Manufacturing Plants of Medicinal Products for Human Use, and with the principles set forth in the guidelines prepared on the basis of this Regulation.

(7) All information, which is relevant to the evaluation of the medicinal product concerned, shall be included in the application, whether favourable or unfavourable to the product. In particular, all relevant details shall be given of any incomplete or abandoned pharmaco-toxicological or clinical test or trial relating to the medicinal product for human use and/or completed trials concerning therapeutic indications not covered by the application.

(8) All clinical trials conducted in Turkey, must fully comply with the requirements of the Regulation on Clinical Trials of Pharmaceuticals and Biological Products. During the assessment of an application, clinical trials, conducted outside Turkey, which relate to medicinal products for human use intended to be used in Turkey, shall be designed, implemented and reported on the basis of good clinical practice and ethical principles which have been set forth in accordance with the principles specified in the relevant Regulation.

(9) **(Amended phrase:OG-24/9/2022-31963)** Pre-clinical (pharmaco-toxicological) studies shall be carried out in conformity with the provisions specified in the Regulation on

Good Laboratory Practice Principles and the Harmonisation of Test Units, Inspection of Good Laboratory Practice and the Control of the Studies published on the Official Gazette dated 9/3/2020, with no. 27516.

(10) All tests performed on animals for experimental and other scientific purposes are carried out within the framework of legal regulations regarding the protection of animals.

(11) In order to monitor the benefit/risk assessment, any new information not in the original application and all pharmacovigilance information shall be submitted to the Agency. After marketing authorization has been granted, any change to the data in the dossier shall be submitted to the Agency, in accordance with the provisions of the relevant guidelines and, if relevant, pharmacovigilance implementations.

This Annex has been divided into three different parts:

Part I describes the application format, the summary of product characteristics, the labelling, the leaflet and presentation requirements for all marketing authorization applications. (Modules 1 to 5).

Part II provides derogation for "Specific applications", i.e well-established medicinal use, essentially similar products, fixed combinations, biosimilar medicinal products, exceptional circumstances, and mixed marketing authorisation applications (part bibliographic and part own studies).

Part III deals with ‘Particular application requirements’ for biological medicinal products (Plasma Master File, PMF); (Vaccine Antigen Master File, VAMF)], radio-pharmaceuticals, herbal medicinal products and allergen products.

PART I

STANDARDISED MARKETING AUTHORISATION DOSSIER REQUIREMENTS

1. MODULE 1: ADMINISTRATIVE INFORMATION

1.1. Table of contents

A comprehensive table of contents of Modules 1 to 5 of the dossier submitted for marketing authorization application shall be presented.

1.2. Application form

The applicant shall submit 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; certified document indicating that the applicant is authorised to submit an application; 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.

The medicinal product, which is the subject of the application, shall be identified by name, name of the active substance(s), together with the pharmaceutical form, the route of administration, strength and the final presentation, including packaging.

The name and address of the applicant shall be given, together with the name and address of the manufacturers and the sites involved in the different stages of the manufacture including the manufacturer of the finished product and the manufacturer(s) of the active substance(s).

The applicant shall identify the type of application.

Annexed to the administrative data shall be other documents of the manufacturing site, as defined in the Regulation Regarding the Manufacturing Plants of Medicinal Products for Human Use, together with a list of countries in which marketing authorisation has been submitted, copies of certified product certificates granted by the other country or countries where the product has been placed on market and the summaries of product characteristics.

As outlined in the application form, the applicants shall provide, details of the medicinal product for human use subject of the application, the proposed marketing authorization holder and information on manufacturing site for all manufacturing steps and information on issues such as the product being in the pediatric development program.

1.3. Summary of product characteristics, Labelling and Package Leaflet

1.3.1. Summary of Product Characteristics

The applicant shall propose a summary of the product characteristics, in accordance with Article 10 of this Regulation.

1.3.2. Labelling and package leaflet

A proposed labelling text for immediate and outer packaging as well as for the package leaflet shall be provided. These shall be in accordance with all the provisions of the relevant legislation on the labelling and package leaflet.

1.3.3. Mock-ups and specimens

The applicant shall provide specimen and/or mock-ups of the immediate and outer packaging, labels and package leaflets for the medicinal product for human use concerned.

1.4. Information About the Experts

In accordance with Article 11 of the Regulation, experts must provide detailed reports of their observations on the documents and particulars which constitute the marketing authorisation dossier and in particular on Modules 3, 4 and 5 (chemical, pharmaceutical and biological documentation, **(Amended phrase:OG-24/9/2022-31963)** nonclinical documentation and clinical documentation, respectively). The experts are required to address the critical points related to the quality of the medicinal product for human use and of the investigations carried out on animals and human beings and bring out all the data relevant for evaluation.

These requirements shall be met by providing a quality overall summary, a **(Amended phrase:OG-24/9/2022-31963)** nonclinical overview (data from studies carried out in animals) and a clinical overview that shall be located in Module 2 of the marketing authorisation application dossier. A declaration signed by the experts together with brief information on their educational background, training and occupational experience shall be presented in Module 1 The experts shall have suitable technical or professional qualifications. The professional relationship of the expert to the applicant shall be declared.

1.5. Specific Requirements for Different Types of Applications

Specific requirements for different types of applications are addressed in Part II of the present Annex.

1.6. Environmental Risk Assessment

Where applicable, applications for marketing authorisations shall include a risk assessment overview evaluating possible risks to the environment due to the use and/or disposal

of the medicinal product for human use and make proposals for appropriate labelling provisions. Environmental risk connected with the release of medicinal products for human use containing or consisting of GMOs (Genetically Modified Organisms) shall be assessed in accordance with the relevant legislation of the Ministry of Agriculture and Forestry.

Information pertaining to the environmental risk shall appear as an appendix to Module 1.

In the presentation of the information, the relevant legislation of the Ministry of Agriculture and Forestry and any guidelines published in relation to this legislation, shall be taken into consideration during the submission of the documents.

The documents to be submitted consist of:

- Introduction,
- any consent of the competent authority pertaining to the deliberate release into the environment of the GMOs for research and development purposes according to the relevant legislation,
- the detection and identification methods of GMOs in accordance with the relevant legislation, GMO codes, plus any additional information on the GMOs or the product of relevance to evaluating of the environmental risk,
- an environmental risk assessment report prepared on the basis of relevant legislation,
- taking into account the above information and the environmental risk assessment report, a conclusion report which proposes an appropriate risk management strategy which includes, as relevant to the GMO and product in question, a post-market monitoring plan and the identification of any special particulars which need to appear in the Summary of Product Characteristics, labelling and package leaflet,
- appropriate measures in order to inform the public,

A statement with a dated signature of the expert, information on the expert's educational, training and occupational experience, and the expert's relationship with the applicant, shall be included in the report submitted.

(Appended:OG-24/9/2022-31963) 1.7. Information on Pharmacovigilance

1.7.1. Pharmacovigilance System

According to the subparagraph (z) of the first paragraph of Article 8 of this Regulation, it must be ensured that the pharmacovigilance system to be introduced by the applicant is defined in detail. In doing so, the requirements and format set out in the Regulation on the Safety of Medicines should be followed.

1.7.2. Risk management system

Detailed description of the risk management system to be created by the applicant according to the sub-paragraph (z) of the first paragraph of Article 8 of this Regulation must be made in the appropriate place. In doing so, the requirements and format laid down in the Regulation on the Safety of Medicines and the Good Pharmacovigilance Practice Guideline must be followed.

(Appended:OG-24/9/2022-31963) 1.8. Information on Clinical Studies

In case clinical trials are conducted outside of Türkiye, the applicant's declaration containing a statement that it meets the ethical requirements set forth in the Regulation on Clinical Trials of Medicines and Biological Products must be submitted. The declaration must include the statement ‘Clinical studies conducted outside Türkiye meet the ethical requirements

of the Regulation on Clinical Trials of Medicines and Biological Products' and should be presented with a list of all experiments (protocol number) and related countries.

2. MODULE 2: SUMMARIES

This Module aims to summarize the chemical, pharmaceutical and biological data, **(Amended phrase:OG-24/9/2022-31963)** nonclinical data and the clinical data presented in Modules 3, 4 and 5 of the dossier for marketing authorisation and to provide the reports/overviews.

Critical points shall be addressed and analyzed. Factual summaries including tabular formats shall be provided. Summaries in tabular format and other information shall provide cross-references to the main documentation presented in Module 3 (chemical, pharmaceutical and biological documentation), Module 4 **(Amended phrase:OG-24/9/2022-31963)** (nonclinical documentation) and Module 5 (clinical documentation).

Information contained in Module 2 shall be presented in accordance with the format, content and numbering system delineated in the CTD Guideline.

The overviews and summaries shall comply with the basic principles and requirements as laid down herewith:

2.1. Overall table of contents

Module 2 shall contain a table of contents for the scientific documentation submitted in Modules 2 to 5.

2.2. Introduction

Information on the pharmacological class, mode of action and proposed clinical use of the medicinal product for human use for which a marketing authorisation is requested shall be supplied.

2.3. Quality Overall Summary

A review of the information related to the chemical, pharmaceutical and biological data shall be provided in a quality overall summary.

Key critical parameters and issues related to quality aspects shall be emphasized as well as justification in cases where the relevant guidelines are not followed. This document shall follow the scope and outline of the corresponding detailed data presented in Module 3.

2.4. (Amended phrase:OG-24/9/2022-31963) Nonclinical Overview

An integrated and critical assessment of the **(Amended:OG-24/9/2022-31963)** nonclinical *in vitro* evaluation of the medicinal product for human use in animals shall be required. Discussion and justification of the testing strategy and of deviation from the relevant guidelines shall be included.

Except for biological medicinal products, an assessment of the impurities and degradation products shall be included along with their potential pharmacological and toxicological effects. The implications of any differences in the chirality, chemical form, and impurity profile between the compound used in the **(Amended phrase:OG-24/9/2022-31963)** nonclinical studies and the medicinal product for human use to be marketed shall be discussed.

For biological medicinal products, comparability of material used in **(Amended phrase:OG-24/9/2022-31963)** nonclinical studies, clinical studies, and the medicinal product for marketing shall be assessed.

Any novel excipient shall be the subject of a specific safety assessment.

The characteristics of the medicinal product for human use, as demonstrated by the **(Amended:OG-24/9/2022-31963)** nonclinical studies shall be defined and the implications of the findings for the safety of the medicinal product for human use for the intended clinical use in humans shall be discussed.

2.5. Clinical Overview

The clinical overview is intended to provide a critical analysis of the clinical data included in the clinical summary and Module 5 The approach to the clinical development of the medicinal product for human use, including critical study design, decisions and assessments related to and performance of the studies shall be provided.

A brief overview of the clinical findings, as well as the benefits and risks based on the conclusions of the clinical studies shall be provided. An interpretation of the way the efficacy and safety findings support the proposed dose and target indications and an evaluation of how the summary of product characteristics and other approaches will optimise the benefits and manage the risks is required.

Efficacy or safety issues encountered in development and unresolved issues shall be explained.

2.6. (Amended:OG-24/9/2022-31963) Summary of Nonclinical Studies

The results of pharmacology, pharmaco-kinetics and toxicology studies carried out in animals and in *vitro* shall be provided as factual written and tabulated summaries which shall be presented in the following order:

- Introduction
- Pharmacology summary
- Pharmacology tabulated summary
- Pharmaco-kinetics summary
- Pharmaco-kinetics tabulated summary
- Toxicology summary
- Toxicology tabulated summary

2.7. Clinical Summary

A detailed, factual summary of the clinical information on the medicinal product for human use included in Module 5 shall be provided. This shall include the results of all bio-pharmaceutics studies, of clinical pharmacology studies, and of clinical efficacy and safety studies. A synopsis of the individual studies is required.

Summarised clinical studies shall be presented in the following order:

— Summary of bio-pharmaceutics and associated analytical methods,

— Summary of clinical pharmacology studies,

— Summary of clinical efficacy,

— Summary of clinical safety,

— Synopses of individual studies.

3. MODULE 3: CHEMICAL, PHARMACEUTICAL AND BIOLOGICAL INFORMATION FOR MEDICINAL PRODUCTS FOR HUMAN USE CONTAINING CHEMICAL OR BIOLOGICAL ACTIVE SUBSTANCES

3.1. Format and Presentation

The general outline of Module 3 is as follows:

A) TABLE OF CONTENTS

B) BODY OF DATA
1) Active substance
a) General Information
- Nomenclature
- Structure
- General Properties
b) Manufacture
- Manufacturing site
- Description of manufacturing process and process controls
- Control of materials
- Controls of critical steps and intermediates
- Process validation or evaluation
- Manufacturing process development
c) Charactherisation
- Elucidation of structure and other characteristics
- Impurities
ç) Control of active substance(s)
- Specifications
- Analytical procedures
- Validation of analytical procedures
- Batch analyses
- Justification of specifications
d) Reference standards or materials
e) Immediate packaging (container closure system)
f) Stability (in line with the guideline on stability tests)
-Stability summary and conclusions
- Post-approval stability protocol and stability commitment
- Stability data
2) Finished product
a) Definition and composition of medicinal products for human use
b) Pharmaceutical development
- Components of the medicinal product for human use
• Active substance(s)
• Excipient(s)
- Medicinal product for human use
• Formulation development
• Overages (Excess) dose
• Physicochemical and biological properties
- Manufacturing process development
- Immediate packaging (container closure system)
- Microbiological attributes
- Compatibility
c) Manufacture
- Manufacturing site(s)

- Batch formula
- Description of manufacturing process and process controls
- Controls of critical steps and intermediates
- Process validation or evaluation

ç) Control of excipient(s)

- Specifications
- Analytical procedures
- Validation of analytical procedures
- Justification of specifications
- Excipients of human or animal origin
- Novel excipients

d) Control of the finished product

- Specifications
- Analytical procedures
- Validation of analytical procedures
- Batch analyses
- Characterisation of impurities
- Justification of specification(s)

e) Reference standards or materials

f) Immediate packaging (container closure system)

g) Stability (in line with the guideline on stability tests)

- Stability summary and conclusions
- Post-approval stability protocol and stability commitment
- Stability data

3) Appendices

- Manufacturing site and equipment (only for biological medicinal products)
- Adventitious agents safety evaluation
- Excipient(s)

4) Other Additional Information

- Process validation scheme for the medicinal product
- Medical device (if used)
- Certificate(s) of suitability to pharmacopoeia, of the active substance(s)
- Medicinal products containing or using in the manufacturing process materials of animal and/or human origin (TSE procedure)

C) LITERATURE REFERENCES

3.2. Contents: Basic Principles and Requirements

The chemical, pharmaceutical and biological data that shall be provided shall include for the active substance(s) and for the finished medicinal product all of relevant information on: the development, the manufacturing process, the characterisation and properties, the quality control operations and requirements, the stability as well as a description of the composition and presentation of the finished medicinal product.

Information dealing with active substance(s) with finished product shall be provided, respectively.

This Module shall in addition supply detailed information on the starting and raw materials used during the manufacturing operations of the active substance(s) and on the excipients incorporated in the formulation of the finished medicinal product.

All the procedures and methods used for manufacturing and controlling the active substance and the finished medicinal product shall be described in sufficient details to enable them to be repeated in control tests, carried out at the request of the Agency. All test methods shall correspond to the state of scientific progress at the time and shall be validated. Results of the validation studies shall be provided. In the case of test procedures included in the pharmacopoeia, this description shall be replaced by the appropriate detailed reference to the monograph(s) and general chapter(s).

The monographs of the Pharmacopoeia shall be applicable to all substances, preparations and pharmaceutical forms appearing in the monographs. In respect of other substances, observance with national pharmacopoeia shall be required. However, where a material in the pharmacopoeia has been prepared by a method liable to leave impurities not controlled in the pharmacopoeia monograph, these impurities and their maximum tolerance limits must be declared and a suitable test procedure must be described. In cases where the specifications contained in the pharmacopoeia might be insufficient to ensure the quality of the substance, the Agency may request more appropriate specifications from the marketing authorization holder. The Agency shall inform the authorities responsible for the pharmacopoeia in question. The applicant shall provide the authorities of that pharmacopoeia with the details of the alleged insufficiency and the additional specifications applied.

In the case of analytical procedures contained in the pharmacopoeia, this description shall be replaced in each relevant section by the appropriate detailed reference to the monograph(s) and general chapter(s).

In case where described starting and raw materials, active substances or excipients are not described in the pharmacopoeia compliance with the pharmacopoeia of a third country can be accepted. In such cases, the applicant shall submit a copy of the monograph accompanied by the validation of the analytical methods contained in the monograph and by a translation where appropriate.

Where the active substance and/or a raw and starting material or excipient(s) are the subject of a monograph of the European Pharmacopoeia, the applicant can apply for a certificate of suitability that, where granted by the European Directorate for the Quality of Medicines, shall be presented in the relevant section of this Module. Those certificates of suitability of the monograph of the European Pharmacopoeia are deemed to replace the relevant data of the corresponding sections described in this Module. The manufacturer shall ensure in writing to the applicant that no changes have been made in the manufacturing process since the issuance of the certificate of suitability by the EDQM.

For a well-defined active substance, the active substance manufacturer or the applicant may arrange for the;

(a) detailed description of the manufacturing process,

(b) quality control of the manufacturing process and,

(c) process validation of the manufacturing process,

to be supplied in a separate document directly to the Agency by the manufacturer of the active substance as an Active Substance Master File.

In this case, however, the manufacturer provides the applicant with all the data that may be necessary for him to take responsibility for the medicinal product.

The manufacturer shall confirm in writing to the applicant that he will ensure batch-to-batch consistency and not modify the manufacturing process and specifications without informing in advance the applicant. Documents and particulars supporting the application for such a change shall be supplied to the Agency. Documents and particulars will be also supplied to the applicant when they concern the open part of the active substance master file.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies (materials from ruminant origin): at each step of the manufacturing process, the applicant must demonstrate the compliance of the materials used with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products and its updates, published by the Commission in the Official Journal of the European Union. Demonstration of compliance with the said Note for Guidance can be done by submitting either, preferably a certificate of suitability to the relevant monograph of the European Pharmacopoeia that has been granted by the European Directorate for the Quality of Medicines or by the supply of scientific data to substantiate this compliance.

For adventitious agents, information assessing the risk with respect to potential contamination with adventitious agents, whether they are non-viral or viral, as laid down in relevant guidelines/communiques as well as in relevant general monograph and general chapter of the pharmacopoeia, shall be provided.

Any special apparatus and equipment, which may be used at any stage of the manufacturing process and control operations of the medicinal product for human use, shall be described in adequate details.

For medical device part of medicinal products for human use with medical devices considered within the scope of this Regulation pursuant to Article 1 of the Regulation on Medical Devices published in the Official Gazette dated 2/6/2021 and numbered 31499, the relevant general safety and performance requirements stated in the Annex 1 of the Regulation on Medical Devices shall apply. An EU Declaration of Conformity or EC Certificate of Conformity is submitted for assessment of compliance with the requirements. If the results of the conformity assessment cannot be submitted and the device is used separately, in case a notified body is required for conformity assessment pursuant to the Medical Device Regulation, for the device type in question, the Agency shall request the applicant to submit an opinion issued by a notified body designated in accordance with the Medical Device Regulation on the conformity of the device part with the relevant requirements.

Special attention shall be paid to the following selected elements.

3.2.1. Active substance(s)

3.2.1.1. General information and information related to the starting and raw materials

a) Information on the nomenclature of the active substance(s) shall be provided, including recommended International Non-proprietary Name (INN), pharmacopoeia name if relevant and chemical name(s).

The structural formula, including relative and absolute stereo-chemistry, the molecular formula and the relative molecular mass shall be provided. For biotechnological medicinal products if appropriate, the schematic amino acid sequence and relative molecular mass shall be provided.

A list shall be provided of physicochemical and other relevant properties of the active substance, including biological activity for biological medicinal products.

b) For the purposes of this Annex, starting materials shall mean all the materials from which the active substance is manufactured or extracted.

For biological medicinal products, starting materials shall mean any substance of biological origin such as micro-organisms, organs and tissues of either plant or animal origin, cells or fluids (including blood or plasma) of human or animal origin, and biotechnological cell constructs (cell substrates, whether they are recombinant or not, including primary cells).

A biological medicinal product is a product, the active substance of which is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control.

The following shall be considered as biological medicinal products:

a) Immunological medicinal products for human use and blood products as defined respectively in paragraphs (o) and (p) of the first paragraph of Article 4 of this Regulation,

b) Advanced therapy medicinal products,

c) Medicinal products for human use developed through one of the following biotechnological processes:

- Recombinant DNA technology,

- Controlled expression of genes encoding biologically active proteins in prokaryotes and eukaryotes, including transformed mammalian cells,

- Hybridoma and monoclonal antibody methods.

Any other substances used for manufacturing or extracting the active substance(s) but from which this active substance is not directly derived, such as reagents, culture media, foetal calf serum, additives, and buffers involved in chromatography, etc. are known as raw materials.

3.2.1.2. Manufacturing process of the active substance(s)

a) The description of the active substance manufacturing process represents the applicant's commitment for the manufacture of the active substance. To adequately describe the manufacturing process and process controls, appropriate information as laid down in the relevant guidelines shall be provided.

b) All materials needed in order to manufacture the active substance(s) shall be listed, identifying where each material is used in the process. Information on the quality and control of these materials shall be provided. Information demonstrating that materials meet standards appropriate for their intended use shall be provided.

Raw materials shall be listed and their quality and controls shall also be documented.

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing shall be provided.

c) For biological medicinal products, the following additional requirements shall apply:

The origin and history of starting materials shall be described and documented.

Regarding the specific measures for the prevention of the Transmission of animal Spongiform Encephalopathies, the applicant must demonstrate that the active substance complies with the Note for Guidance on Minimising the Risk of Transmitting Animal

Spongiform Encephalopathy Agents via Medicinal Products and its updates, published by the Commission in the Official Journal of the European Union.

When cell banks are used, the cell characteristics shall be shown to have remained unchanged at the passage level used for the production and beyond.

Seed materials, cell banks, pools of serum or plasma and other materials of biological origin and, whenever possible, the materials from which they are derived shall be tested for adventitious agents.

If the presence of potentially pathogenic adventitious agents is inevitable, the corresponding material shall be used only when further processing ensures their elimination and/or inactivation, and this shall be validated. Whenever possible, vaccine production shall be based on a seed lot system and on established cell banks. For bacterial and viral vaccines, the characteristics of the infectious agent shall be demonstrated on the seed. In addition, for live vaccines, the stability of the attenuation characteristics shall be demonstrated on the seed. If this proof is not sufficient, the attenuation characteristics shall also be demonstrated at the production stage.

For medicinal products derived from human blood or plasma, the origin and the criteria and procedures for collection, transportation and storage of the starting material shall be described and documented in accordance with provisions laid down in Part III of this Annex.

The manufacturing facilities and equipment shall be described.

ç) Tests and acceptance criteria carried out at every critical step, information on the quality and control of intermediates and process validation and/or evaluation studies shall be provided as appropriate.

d) If the presence of potentially pathogenic adventitious agents is inevitable, the corresponding material shall be used only when further processing ensures their elimination and/or inactivation, and this shall be validated.

e) A description and discussion of the significant changes made to the manufacturing process during development and/or manufacturing site of the active substance(s) shall be provided.

3.2.1.3. Characterization of the active substance (s)

Data highlighting the structure and other characteristics of the active substance(s) shall be provided.

Confirmation of the structure of the active substance(s) based on any physico-chemical and/or immuno-chemical and/or biological methods, as well as information on impurities shall be provided.

3.2.1.4. Control of active substance(s)

Detailed information on the specifications used for routine control of active substance(s), justification for the choice of these specifications, methods of analysis and their validation shall be provided.

The results of control carried out on individual batches manufactured during development shall be presented.

3.2.1.5. Reference standards or materials

Reference preparations and standards shall be identified and described in detail. Where relevant, chemical and biological reference material of the pharmacopoeia shall be used.

3.2.1.6. Container and closure system of the active substance(s)

A description of the container and the closure system and their specifications shall be provided.

3.2.1.7. Stability of the active substance(s)

In line with the guideline on stability tests:

a) The types of studies conducted, protocols used, and the results of the studies shall be summarised.

b) Detailed results of the stability studies, including information on the analytical procedures used to generate the data and validation of these procedures shall be presented in an appropriate format.

c) The post marketing authorization stability protocol and stability commitment shall be provided.

3.2.2. Finished medicinal product

3.2.2.1. Description and composition of the finished medicinal product

A description of the finished medicinal product and its composition shall be provided. The information shall include the description of the pharmaceutical form and composition with all the constituents of the finished medicinal product, their amount on a per-unit basis, the function of the constituents of:

- Active substance(s),
- the constituent(s) of the excipients, whatever their nature or the quantity used, including colouring matter, preservatives, adjuvants, stabilisers, thickeners, emulsifiers, flavouring and aromatic substances, etc.,
- the constituents of the medicinal product for human use, intended to be ingested or otherwise administered to the patient, of the outer covering of the medicinal products (hard capsules, soft capsules, rectal capsules, coated tablets, films-coated tablets, etc.),
- these particulars shall be supplemented by any relevant data concerning the type of container and, where appropriate, its manner of closure, together with details of devices with which the medicinal product will be used or administered and which will be delivered with the medicinal product.

Within the scope of the usual terminology, to be used in describing the structure of medicinal products for human use;

- in respect of substances, reference shall be made to the pharmacopoeia concerned, with the main title at the head of the monograph in question.
- in respect of other substances, the common name, or failing this, an exact scientific designation shall be described by a statement of how and from what they were prepared, supplemented, where appropriate, by any other relevant details,
- in respect of colouring matter, designation by the ‘E’ code assigned to them in the Turkish Food Codex Regulation on Specifications of Food Additives published in the Official Gazette dated 3/4/2017 and numbered 30027 shall be used. In addition, it must meet the criteria set out in the same Regulation. In order to give the quantitative composition of the active substance(s) of the finished medicinal products, it is necessary, depending on the pharmaceutical form concerned, to specify the mass, or the number of units of biological activity, either per dosage-unit or per unit of mass or volume, of each active substance.

Active substance(s) present in the form of compounds or derivatives shall be designated quantitatively by their total mass, and if necessary or relevant, by the mass of active entity or entities of the molecule.

For medicinal products containing an active substance, which is the subject of an application for marketing authorisation, the quantitative statement of an active substance, which is a salt or hydrate shall be systematically expressed in terms of the mass of the active entity or entities in the molecule.

Units of biological activity shall be used for substances which cannot be defined molecularly. Where an International Unit of biological activity has been defined by the World Health Organisation, this shall be used. Where no International Unit has been defined, the units of biological activity shall be expressed in such a way as to provide unambiguous information on the activity of the substances by using where applicable the European Pharmacopoeia Units.

3.2.2.2. Pharmaceutical development

This chapter shall be devoted to information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, immediate packaging (container closure system), microbiological attributes and usage instructions are appropriate for the intended use specified in the marketing authorisation application dossier. The studies described in this section are distinct from routine control tests conducted according to specifications. Critical parameters of the formulation and process attributes that can influence batch reproducibility, medicinal product for human use performance and medicinal product quality shall be identified and described. Additional supportive data, where appropriate, shall be referenced to the relevant sections of Module 4 **(Amended phrase: OG-24/9/2022-31963)** (Nonclinical Study Reports) and Module 5 (Clinical Study Reports) of the marketing authorization application dossier.

a) The compatibility of the active substance with excipients as well as key physicochemical characteristics of the active substance that can influence the performance of the finished product or the compatibility of different active substances with each other in the case of combination products, shall be documented.

b) The choice of the excipient(s), in particular relative to their respective functions and concentration shall be documented.

c) A description of the development of the finished product shall be provided, taking into consideration the proposed route of administration and usage.

ç) Any overage(s) in the formulation(s) shall be warranted.

d) As far as the physiochemical and biological properties are concerned, any parameter relevant to the performance of finished product shall be addressed and documented.

e) The selection and optimization of the manufacturing process as well as differences between the manufacturing process(es) used to produce pivotal clinical batches and the process used for manufacturing the proposed finished medicinal product shall be provided.

f) The suitability of the immediate packaging (container/closure system) used for the storage, shipping and use of the finished product shall be documented. A possible interaction between medicinal product for human use and container may need to be considered.

g) The microbiological attributes of the dosage form in relation with non-sterile and sterile products shall be in accordance with and documented as prescribed in the pharmacopoeia.

ğ) In order to provide appropriate and supportive information for the labelling the compatibility of the finished product with reconstitution diluent(s) or dosage devices shall be documented.

3.2.2.3. Manufacturing process of the finished medicinal product

a) The description of the manufacturing method accompanying the application for Marketing authorization pursuant to the first paragraph of Article 8 this Regulation, shall be drafted in such a way as to give an adequate synopsis of the nature of the operations employed and shall include at least:

- mention of the various stages of manufacture including process controls and corresponding acceptance criteria, so that an assessment can be made of whether the processes employed in producing the pharmaceutical form might have produced a change in the constituents,
- in case of continuous manufacture, specification of full details concerning the precautions taken to ensure the homogeneity of the finished product,
- experimental studies validating the manufacturing process, where a non-standard method of manufacture is used or where it is critical for the medicinal product for human use,
- for sterile medicinal products for human use, details of the sterilisation processes and/or aseptic procedures used,
- a detailed batch formula.

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing shall be provided.

b) Particulars relating to the product control tests that may be carried out at an intermediate stage of the manufacturing process, with a view to ensuring the consistency of the production process shall be included.

These tests are essential for checking the conformity of the medicinal product with the formula when, exceptionally, an applicant proposes an analytical method for testing the finished product which does not include the assay of all the active substances (or of all the excipient constituents subject to the same requirements as the active substances).

The same applies where the quality control of the finished product depends on in-process control tests, particularly if the medicinal product is essentially defined by its method of preparation.

c) Description, documentation, and results of the validation studies for critical steps or critical assays used in the manufacturing process shall be provided.

3.2.2.4. Control of excipient(s)

a) All the materials needed in order to manufacture the excipient(s) shall be listed identifying where each material is used in the process. Information on the quality and control of these materials shall be provided. Information demonstrating that materials meet standards appropriate for their intended use shall be provided.

In respect of colouring matter, designation by the ‘E’ code assigned to them in the Turkish Food Codex Regulation on Specifications of Food Additives shall be used. In addition, it shall meet the criteria set out in the same Regulation.

b) For each excipient, the specifications and their justifications shall be detailed. The analytical procedures shall be described and duly validated.

c) Specific attention shall be paid to excipients of human or animal origin.

Regarding the specific measures for the prevention of the Transmission of animal Spongiform Encephalopathies, the applicant must demonstrate also for excipients that the medicinal product for human use is manufactured in accordance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products and its updates, published by the Commission in the Official Journal of the European Union. Demonstration of compliance with the aforementioned Note for Guidance can be done by submitting either preferably a certificate of suitability to the relevant monograph on Transmissible Spongiform Encephalopathies of the European Pharmacopoeia, or by the supply of scientific data to substantiate this compliance.

ç) Novel excipient(s):

For excipient(s) used for the first time in a medicinal product or by a new route of administration, full details of manufacture, characterisation, and controls, with cross references to supporting safety data, both **(Amended phrase:OG-24/9/2022-31963)** nonclinical and clinical, shall be provided according to the active substance format previously described.

A document containing the detailed chemical, pharmaceutical and biological information shall be presented. This information shall be formatted in the same order as the chapter devoted to Active Substance(s) of Module 3.

Information on novel excipient(s) may be presented as a stand-alone document following the format described in the former paragraphs. Where the applicant differs from the novel excipient manufacturer the said stand-alone document shall be made available to the applicant for submission to the Agency.

Additional information on toxicity studies of new excipient(s)shall be provided in Module 4 of the dossier.

Clinical studies shall be provided in Module 5.

3.2.2.5. Control of the finished medicinal product

For the control of the finished medicinal product, a batch of a medicinal product for human use is an entity which comprises all the units of a pharmaceutical form which are made from the same initial quantity of material and have undergone the same series of manufacturing and/or sterilisation operations or, in the case of a continuous production process, all the units manufactured in a given period of time.

Unless there is appropriate justification, the maximum acceptable deviation in the active substance content of the finished product shall not exceed ± 5 % at the time of manufacture.

Detailed information on the specifications, (release and shelf life) justification for their choice, methods of analysis and their validation shall be provided.

3.2.2.6. Reference standards or materials

Reference preparations and standards used for testing of the finished medicinal product shall be identified and described in detail, if not previously provided in the section related to the active substance(s).

3.2.2.7. Immediate packaging (container and closure) system of the finished medicinal product

A description of the container and the closure system including the identity of each immediate packaging material and their specifications shall be provided. The specifications shall include description and identification. Non-pharmacopoeial methods (with validation) shall be included where appropriate.

For non-functional outer packaging materials only a brief description shall be provided. For functional outer packaging materials additional information shall be provided.

3.2.2.8. Stability of the finished product

In line with the guideline on stability tests:

a) The types of studies conducted, protocols used and the results of the studies shall be summarized;

b) Detailed results of the stability studies, including information on the analytical procedures used to generate the data and validation of these procedures shall be presented in an appropriate format. In case of vaccines, information on cumulative stability shall be provided where appropriate.

c) The post marketing authorization stability protocol and stability commitment shall be provided.

4. MODULE 4: (Amended phrase:OG-24/9/2022-31963) NONCLINICAL REPORTS

4.1. Format and Presentation

The general outline of Module 4 is as follows:

A - TABLE OF CONTENTS

B -STUDY REPORTS

1- Pharmacology

- Primary Pharmaco-dynamics
- Secondary Pharmaco-dynamics
- Safety pharmacology
- Pharmaco-dynamic interactions

2 - Pharmaco-kinetics

- Analytical Methods and Validation Reports
- Absorption
- Distribution
- Metabolism
- Excretion
- **(Amended phrase:OG-24/9/2022-31963)** Nonclinical pharmaco-kinetic interactions
- Other Pharmaco-kinetic Studies

3- Toxicology

a) Single-dose toxicity

b) Repeated dose toxicity

c) Genotoxicity

- *In vitro*
- *In vivo* (including supportive toxicokinetic assessments)

ç) Carcinogenicity

- Long-Term studies
- Short- or Medium-Term Studies

- Other studies

d) Reproductive and Developmental Toxicity

- Fertility and early embryonic development
- Embryo/fetal development
- Prenatal and Postnatal Development
- Studies in which the offspring (juvenile animals) are dosed and/or further evaluated

e) Local tolerance

4 -Other Toxicity Studies

- Antigenicity
- Immunotoxicity
- Mechanistic studies
- Dependence
- Metabolites
- Impurities
- Other

C - LITERATURE REFERENCES

4.2. Contents: Basic Principles and Requirements

Special attention shall be paid to the following elements:

(1) The pharmacological and toxicological tests must show:

a) The potential toxicity of the medicinal product for human use and any dangerous or undesirable toxic effects that may occur under the proposed conditions of use in human being should be evaluated in relation to the pathological condition concerned.

b) The pharmacological properties of the medicinal product for human use, shall be presented in both qualitative and quantitative relationship to the proposed use in human beings. All results must be reliable and of general applicability. Whenever appropriate, mathematical and statistical procedures shall be used in designing the experimental methods and in evaluating the results.

Additionally, it is necessary for clinicians to be given information about the therapeutic and toxicological potential of the product.

(2) For biological medicinal products such as immunological medicinal products for human use and medicinal products derived from human blood or plasma, the requirements may have to be adapted for individual products; therefore the testing program carried out shall be justified by the applicant.

In establishing the testing program, the following shall be taken into consideration:

All tests requiring repeated administration of the medicinal product for human use shall be designed to take account of the possible induction of, and interference by, antibodies.

Examination of reproductive function, of embryo/foetal and peri-natal toxicity, of mutagenic potential and of carcinogenic potential shall be considered. Where constituents other than the active substance(s) are incriminated, validation of their removal may replace the study.

(3) The toxicology and pharmaco-kinetics of an excipient used for the first time in the pharmaceutical field shall be investigated.

(4) Where there is a possibility of significant degradation during storage of the medicinal product for human use, the toxicology of degradation products must be considered.

4.2.1. Pharmacology

Pharmacology study shall follow two distinct lines of approach:

- Firstly, the actions relating to the proposed therapeutic use shall be adequately investigated and described. Where possible, recognised and validated assays, both *in vivo* and *in vitro* shall be used. Novel experimental techniques must be described in such detail as to allow them to be reproduced. The results shall be expressed in quantitative terms using, for example, dose-effect curves, time-effect curves, etc. Wherever possible, comparisons shall be made with data relating to a substance or substances with a similar therapeutic action.

- Secondly, the applicant shall investigate the potential undesirable pharmaco-dynamic effects of the substance on physiological functions. These investigations shall be performed at exposures in the anticipated therapeutic range and above. The experimental techniques, unless they are standard procedures, must be described in such detail as to allow them to be reproduced, and the investigator must establish their validity. Any suspected modification of responses resulting from repeated administration of the substance shall be investigated.

For the pharmaco-dynamic medicinal product interaction, tests on combinations of active substance(s) may be prompted either by pharmacological premises or by indications of therapeutic effect. In the first case, the pharmaco-dynamic study shall demonstrate those interactions, which might make the combination of value in therapeutic use. In the second case, where scientific justification for the combination is sought through therapeutic experimentation, the investigation shall determine whether the effects expected from the combination can be demonstrated in animals, and the importance of any collateral effects shall at least be investigated.

4.2.2. Pharmacokinetics

Pharmacokinetics refers to studies that examine the status of the active substance(s) and their metabolites in the organism and covers the absorption, distribution, metabolism (biotransformation) and excretion of these substances.

The study of these different phases may be carried out mainly by means of physical, chemical or possibly biological methods and by observation of the actual pharmacodynamic activity of the substance itself.

Information on distribution and elimination shall be necessary in all cases where such data are indispensable to determine the dosage for humans and in respect of chemotherapeutic substances (antibiotics, etc.) and substances whose use depends on their non-pharmacodynamic effects (e.g. numerous diagnostic agents, etc.).

In vitro studies may also be carried out with the advantage of using human material for comparison with animal material (i.e. protein binding, metabolism, drug-drug interaction).

All substances with pharmacological activity must be investigated in terms of pharmacokinetics. For new combinations of known substances that have been investigated in accordance with the provisions of this Regulation, pharmacokinetic studies may not be required when justified by toxicity tests and therapeutic trials.

The pharmacokinetic program shall be designed to allow comparison between humans and animals and extrapolation of the information obtained.

4.2.3. Toxicology

a) Single-dose toxicity

Single-dose toxicity test refers to the qualitative and quantitative studies of the toxic reactions that may result from only one application of the active substance(s) in the human

medicinal product, in the proportions they are present in the human medicinal product and in the physicochemical condition.

Single-dose toxicity test is carried out in accordance with the relevant guidelines determined by the Agency.

b) Repeated dose toxicity

The purpose of repeated-dose toxicity tests is to reveal the physiological or anatomical and pathological changes resulting from repeated administration of the active substance or combination of active substance under investigation and to determine the connection of these changes with dosage.

Generally, it is desirable that two tests be performed; one short-term, lasting two to four weeks, the other long-term. The duration of the latter shall depend on the conditions of clinical use. Its purpose is to describe potential adverse effects to which attention should be paid in clinical studies. The duration of the test must comply with the relevant guidelines determined by the Agency.

c) Genotoxicity

The aim of studies on mutagenic and clastogenic potential is to reveal the changes that substances can create in the genetics of individuals or cells. Mutagenic substances may present a hazard to health since exposure to a mutagen carries the risk of inducing germ-line mutation, with the possibility of inherited disorders and the risk of somatic mutations including those leading to cancer. The conduct of these studies is obligatory for any new substance.

ç) Carcinogenicity

Tests to reveal carcinogenic effects shall normally be required:

1. These studies shall be performed for any medicinal product for human use whose expected clinical use is for a prolonged period of a patient’s life, either continuously or repeatedly in an intermittent manner.

2. These studies are recommended for some medicinal products for human use if there is concern about their carcinogenic potential, such as from products of the same class or similar structure or from evidence in repeated dose toxicity studies.

3. Studies with unequivocally genotoxic compounds are not needed, as they are presumed to be trans-species carcinogens, implying a hazard to humans. If such a medicinal product for human use is intended to be administered on a chronic basis to humans, a chronic study may be necessary to detect early tumorigenic effects.

d) Reproductive and Developmental Toxicity

Investigation of possible impairment of male or female reproductive function as well as harmful effects on progeny shall be performed by appropriate tests.

These tests comprise studies of the effect on adult male or female reproductive function, studies of the toxic and teratogenic effects at all stages of development from conception to sexual maturity as well as latent effects when the medicinal product for human use under investigation has been administered to the female during pregnancy.

Conduct of these tests must be adequately justified.

Depending on the established indication of the medicinal product for human use, additional studies showing improvements when administered to the neonate may be warranted.

Embryo/fetal toxicity studies shall normally be conducted on two mammalian species, one of which shall be other than a rodent. Perinatal and postnatal studies shall be conducted in

at least one species. If the metabolism of a medicinal product for human use in particular species is known to be similar to that in man, it is desirable to include this species. It is also desirable that one of the species is the same as in the repeated dose toxicity studies.

The state of scientific knowledge at the time when the application is lodged shall be taken into account when determining the study design.

e) Local tolerance

The purpose of local tolerance studies is to ascertain whether medicinal products for human use (both active substance(s) and excipient(s)) are tolerated at sites in the body, which may come into contact with the medicinal product as a result of its administration in clinical use. The testing strategy shall be such that any mechanical effects of administration or purely physicochemical actions of the product can be distinguished from toxicological or pharmacodynamic ones.

Local tolerance testing shall be conducted with the preparation being developed for human use, using the vehicle and/or excipients in treating the control groups.

The design of local tolerance tests (choice of species, duration, frequency, route of administration and doses) will depend upon the problem to be investigated and the proposed conditions of administration in clinical use. Reversibility of local lesions shall be performed where relevant.

Validated *in vitro* tests may be performed instead of animal studies, provided that the test results are of comparable quality and useful for safety assessment.

For chemicals applied to the skin (e.g. dermal, rectal, vaginal) the sensitizing potential shall be evaluated in at least one of the test systems currently available (the guinea pig assay or the local lymph node assay).

5. MODULE 5: CLINICAL STUDY REPORTS

5.1. Format and Presentation

The general outline of Module 5 is as follows:

A - Table of Contents for Clinical Study Reports

B - Tabular Listing of All Clinical Studies

C - Clinical study reports

1- Reports of Bio-pharmaceutical Studies

- Bioavailability Study Reports
- Comparative Bioavailability and Bioequivalence Study Reports
- *In vitro-In vivo* Correlation Study Reports
- Reports of Bioanalytical and Analytical Methods

2 - Reports of Studies Pertinent to Pharmacokinetics Using Human Bio-materials

- Plasma Protein Binding Study Reports
- Hepatic Metabolism Reports and Interaction Study Reports
- Reports of Studies Using Other Human Bio-materials

3 - Reports of Human Pharmacokinetic Studies

- Healthy Subjects' Pharmacokinetics and Initial Tolerability Study Reports
- Patients' Pharmacokinetics and Initial Tolerability Study Reports
- Intrinsic Factor Pharmacokinetic Study Reports
- Extrinsic Factor Pharmacokinetic Study Reports
- Population Pharmacokinetic Study Reports

4- Reports of Human Pharmacodynamic Studies

- Healthy Subjects' Pharmacodynamic and Pharmacokinetic/Pharmacodynamic Study Reports

- Patients' Pharmacodynamic and Pharmacokinetic/Pharmacodynamic Studies Study Reports

5 - Efficacy and Safety Study Reports

- Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication

- Study Reports of Uncontrolled Clinical Studies

- Reports of Analyses of Data from More than One Study including any formal integrated analyses, meta-analyses and bridging analyses

- Other Study Reports

6- Reports of Post-Marketing Experience

C - Literature References

5.2. Contents: Basic Principles and Requirements

The following are particularly important:

a) Pursuant to subparagraphs (j), (k) and (l) of the first paragraph of the 8th article of this Regulation and the first paragraph of the 9th article, it should allow the formation of a well-founded and scientifically valid opinion showing whether the clinical information to be provided meets the criteria for the registration of the medicinal product for human use. As a result, all positive or negative results of clinical trials must be reported.

b) Clinical trials must always be preceded by adequate pharmacological and toxicological tests, carried out on animals in accordance with the requirements of Module 4 of this Annex. The investigator should have knowledge of the results obtained from pharmacological and toxicological tests. The applicant must therefore provide the investigator's brochure with all known relevant information prior to initiation of the clinical trial and the data necessary to justify the nature, scale and duration of the proposed trial, including chemical, pharmaceutical and biological data, toxicological, pharmacokinetic and pharmacodynamic data in animals, and data from previous clinical studies The complete pharmacological and toxicological reports shall be provided upon request. For materials of human or animal origin, all available means shall be employed to ensure safety from transmission of infectious agents prior to the commencement of the trial.

c) Marketing authorization holders must arrange for essential clinical trial documents (including case report forms) other than the volunteer's medical files.

- Data holders must keep the data for at least 14 (fourteen) years pursuant to the completion or discontinuation of the trial.

- Relevant documents shall be kept for at least five years pursuant to the completion or discontinuation of the trial.

- Volunteer's medical files should be retained in accordance with applicable legislation and in accordance with the maximum period of time permitted by the hospital, Agency or private practice.

However, the documents can be retained for a longer period, if required by the applicable regulatory requirements or by agreement with the sponsor. It is the responsibility of the sponsor to inform the hospital, Agency or practice as to when these documents no longer need to be retained.

The sponsor or data holders shall retain all other documentation pertaining to the trial as long as the product is authorized. This documentation shall include: the protocol including the rationale, objectives and statistical design and methodology of the trial, with conditions under which it is performed and managed and details of the investigational product, the reference medicinal product and/or the placebo used; standard operating procedures; all written opinions on the protocol and procedures; the investigator's brochure; case report forms on each trial subject; final report; audit certificate(s), if available. The final report shall be retained by the sponsor or subsequent owner, for five years pursuant to the medicinal product for human use is no longer authorized.

The applicant makes the necessary additional arrangements to ensure the archiving of documents and the implementation of the guidelines to be prepared based on this Regulation, in accordance with the provisions of the Regulation on Clinical Trials of Pharmaceuticals and Biological Products.

Any change of ownership of the clinical data shall be documented.

All documents are submitted if requested by the Agency.

ç) The documents belonging to each clinical study must be at a level sufficient to make an objective decision:

-The protocol, including the rationale, objectives and statistical design and methodology of the trial, with conditions under which it is performed and managed and details of the investigational medicinal product used;

- Audit certificate(s), if available;

- The list of the investigator(s) and each investigator shall give his name, address, appointments, curriculum vitae, and the documents indication the distribution of the clinical duties, specify where the trial was carried out, and assemble the information in respect of each patient individually (including case report forms on each volunteer;

- Final report signed by the investigator and for multi-center trials, by all the investigators or the coordinating (principal) investigator,

d) It shall be sufficient to submit the final report of the clinical trial during the application. However, in case the abovementioned information and documents are requested, they shall be kept ready to be submitted to the Agency.

In his conclusions regarding the experimental evidence, the investigator provides an opinion on the safety, tolerance, and efficacy of the product in normal use, as well as useful information on indications and contraindications, dosage and mean duration of treatment, special precautions to be taken in treatment, and clinical symptoms in overdose. In reporting the results of a multi-center study, the principal investigator shall, in his conclusions, express an opinion on the safety and efficacy of the investigational medicinal product for human use on behalf of all centers.

e) The clinical observations of each trial are summarized by stating the following:

1) The number and sex of subjects treated,

2) The selection and age-distribution of the groups of patients being investigated and the comparative tests,

3) The number of patients withdrawn prematurely from the trials and the reasons for such withdrawal,

4) where controlled trials were carried out under the above conditions, whether the control group:

- received any treatment
- received any placebo
- received another medicinal product of known effect
- received treatment other than therapy using medicinal products

5) Frequency of observed adverse reactions,

6) Details concerning patients who may be at increased risk, e.g. elderly people, children, women during pregnancy or menstruation, or whose physiological or pathological condition requires special consideration,

7) Efficacy parameters or evaluation criteria and the results obtained according to these parameters,

8) a statistical evaluation of the results when this is called for by the design of the trials and the variable factors involved.

f) In addition, the investigator shall always indicate his observations on:

1) Any signs of habituation, addiction or difficulty in weaning patients from the medicinal product for human use;

2) Any interactions that have been observed with other medicinal products for human use administered concomitantly;

3) the criteria determining exclusion of certain patients from the trials,

4) any deaths which occurred during the trial or within the follow-up period,

g) Documents relating to a new combination of medicinal substances must be the same as those required for new medicinal products and must prove the safety and efficacy of the combination.

ğ) The reasons for the partially or completely extracted data should be explained. If unexpected results occur during the investigation, further **(Amended phrase:OG-24/9/2022-31963)** preclinical toxicological and pharmacological tests are performed and reviewed.

h) If the medicinal product for human use is intended for long-term administration, particulars shall be given of any modification of the pharmacological action following repeated administration, as well as the establishment of long-term dosage.

5.2.1. Reports of Biopharmaceutical Studies

Bioavailability study reports, comparative bioavailability, bioequivalence study reports, *in vitro* and *in vivo* correlation study reports, bioanalytical and analytical methods are provided.

In addition, evaluations regarding bioavailability are carried out when necessary to demonstrate the bioequivalence of medicinal products for human use specified in the first paragraph of Article 9 of this Regulation.

5.2.2. Reports of Pharmacokinetic Studies using Human Bio-materials

Human biomaterials in this annex refer to proteins, cells, tissues and related substances of human origin that are used *in vitro* or *ex vivo* to determine the pharmacokinetic properties of a medicine substance.

In this context, reports of plasma protein binding studies, hepatic metabolism and active substance interaction studies and studies using other human bio-materials shall be provided.

5.2.3. Reports of Human Pharmacokinetic Studies

a) The following pharmacokinetic properties are defined

- absorption (rate and degree),
- distribution
- metabolism
- excretion

Features of clinical importance are identified, including the meaning of kinetic data for dosing regimens for patients particularly at risk, and the differences between human and **(Amended phrase:OG-24/9/2022-31963)** preclinical animal species.

In addition to standard multiple-sample pharmacokinetic studies, population pharmacokinetic analyses based on sparse sampling during clinical studies can also address questions about the contributions of intrinsic and extrinsic factors to the variability in the dose-pharmacokinetic response relationship. Reports of pharmacokinetic and initial tolerability studies in healthy subjects and patients, reports of pharmacokinetic studies to assess effects of intrinsic and extrinsic factors and reports of population pharmacokinetic studies shall be provided.

b) If the medicinal product is normally to be administered concomitantly with other medicinal products for human use, particulars shall be given of joint administration tests performed to demonstrate possible modification of the pharmacological action.

Pharmacokinetic interactions between the active substance(s) and other medicinal products for human use or substances shall be investigated.

5.2.4. Reports of Human Pharmacodynamic Studies

a) The pharmacodynamic effect associated with efficacy includes the following information:

- the dose-response relationship and its time course,
- justification for the dosage and conditions of administration,
- the mode of action, if possible.

The pharmacodynamic effect not related to efficacy shall be described.

The demonstration of pharmacodynamic effects in human beings shall not in itself be sufficient to justify conclusions regarding any particular potential therapeutic effect.

b) If the medicinal product is normally to be administered concomitantly with other medicinal products for human use, particulars shall be given of joint administration tests performed to demonstrate possible modification of the pharmacological action.

Pharmacodynamic interactions between the active substance(s) and other medicinal products for human use or substances shall be investigated.

5.2.5 - Efficacy and Safety Study Reports

5.2.5.1. Study reports of controlled clinical studies pertinent to the claimed indication

In general, clinical trials shall be conducted as “controlled clinical trials” if possible. These studies shall be randomized, in comparison with placebo and an established medicinal product for human use of proven therapeutic value, where possible. Other study designs are justified. Treatments of control groups differ from case to case, ethical considerations, and therapeutic area. Thus it may, in some instances, be more pertinent to compare the efficacy of a new medicinal product for human use with that of an established medicinal product of proven therapeutic value rather than with the effect of a placebo.

(1) Whenever possible, and especially in studies where the effect of the product cannot be measured objectively, measures to prevent subjective biases, including randomization methods and blinding methods, should be taken.

(2) The protocol of the trial must include a thorough description of the statistical methods to be employed, the number and reasons for inclusion of patients (including calculations of the power of the trial), the level of significance to be used and a description of the statistical unit. Measures taken to avoid bias, particularly methods of randomization, shall be documented. The inclusion of a large number of subjects in a trial must not be regarded as an adequate substitute for a properly controlled trial.

The safety data shall be reviewed taking into account relevant guidelines, with particular attention to events resulting in changes of dose or need for concomitant medication, serious adverse events, events resulting in withdrawal and deaths. Any patients or patient groups at increased risk shall be identified and particular attention paid to potentially vulnerable patients who may be present in small numbers, e.g., children, pregnant women, frail elderly, people with marked abnormalities of metabolism or excretion etc. The results of the safety assessments regarding the possible uses of the medicinal product for human use are disclosed.

5.2.5.2. Study reports of uncontrolled clinical studies reports of analyses of data from more than one study and other clinical study reports

These reports must be submitted.

5.2.6. Reports of post-marketing experience

If the medicinal product for human use is already authorized in third countries, the information shall be given in respect of adverse reactions of the medicinal product for human use concerned and medicinal products containing the same active substance(s), in relation to the usage rates if possible.

5.2.7. Case Report Forms and Individual Patient Lists

When submitted in accordance with the relevant Guideline, case report forms and individual patient data listings shall be provided and presented in the same order as the clinical study reports and indexed by study.

SECTION II

SPECIFIC MARKETING AUTHORIZATION DOSSIERS AND REQUIREMENTS

Some medicinal products for human use contain specific features that require adaptation of all the requirements of the registration application dossier set out in Part I of this Annex. Applicants shall present the dossier upon consideration of these particular situations.

1. ESTABLISHED MEDICAL USE

As specified in the second sub-clause of sub-clause (a) of the first paragraph of Article 9 of this Regulation, the following issues are valid for medicinal products for human use containing active substance(s) with "established medical use", known efficacy and acceptable safety level.

The applicant submits Modules 1, 2 and 3 described in Part I of this annex.

A detailed scientific bibliography is provided for modules 4 and 5, which covers **(Amended phrase:OG-24/9/2022-31963)** nonclinical and clinical features.

The following specific rules shall apply in order to demonstrate the established medicinal use:

a) Factors which have to be taken into account in order to establish a established medicinal use of constituents of medicinal products for human use are:

- the time over which a substance has been used,
- quantitative aspects of the use of the substance,
- the degree of scientific interest in the use of the substance (reflected in the published scientific literature) and
- the coherence of scientific assessments.

Therefore, different periods of time may be necessary for establishing well-established use of different substances. In any case, however, the period of time required for establishing an established medicinal use of a constituent of a medicinal product for human use must not be less than 10 (ten) years from the first systematic and documented use of that substance as a medicinal product.

b) Documentation submitted by the applicant should cover all aspects of safety or efficacy assessments. Relevant literature summaries are found or cited, taking into account pre- and post-marketing studies and the published scientific literature on experiences presented as epidemiological studies, particularly comparative epidemiological studies. All positive and negative documents must be submitted. With respect to the provisions on "established medicinal use", it is in particular necessary to clarify that not just data related to tests and trials but also other evidences are indicated as "bibliographic reference" (post-marketing studies, epidemiological studies, etc.). If the use of such sources of information in the application is appropriately justified, it can be accepted as valid evidence for the safety and efficacy of the product.

c) Particular attention should be given to missing information and justification should be provided as to why an acceptable level of safety or efficacy can be demonstrated despite the lack of studies.

ç) **(Amended phrase:OG-24/9/2022-31963)** Nonclinical or clinical overview explains the link between the information of a medicinal product for human use other than the medicinal product intended to be marketed, and the product applied for. A judgement must be made whether the medical product for human use considered can be regarded as similar to the product for which a marketing authorization application has been submitted, in spite of the existing differences.

d) Post-marketing experience in medicinal products for human use containing the same components is particularly important and applicants should pay special attention to this issue.

2. ESSENTIALLY SIMILAR MEDICINAL PRODUCTS FOR HUMAN USE

a) Applications based on the first sub-clause of the first subparagraph (a) of the first paragraph of Article 9 of this Regulation (basically similar products) contains the data specified in Modules 1, 2 and 3 and Part I of this annex, provided that the application made by the marketing authorization holder of the reference medicinal product for human use to the applicant is allowed to make reference to the information contained in Modules 4 and 5.

b) Applications made based on the fourth sub-clause (a) of the first paragraph of Article 9 of this Regulation (basically similar products, eg generic medicinal products) include data described in Modules 1, 2 and 3 of the section of this Annex, in addition to data showing bioavailability and bioequivalence with the reference medicinal product, provided that the

reference medicinal product for human use is not a biological medicinal product (see Chapter II, 4 Biosimilar medicinal products)

In particular, the following should be noted in the preclinical/clinical overview/summaries of these products:

- The grounds for claiming essential similarity,

- A summary of impurities present in batches of the active substance(s) proposed to be used in the product to be marketed and finished medicinal products (and where relevant, decomposition products arising in products during storage) and an evaluation of these impurities,

- Evaluation of bioequivalence studies or the reasons why the studies were not carried out in accordance with the provisions of the applicable Bioavailability and Bioequivalence legislation,

- It is acceptable to update the published literature related to the active substance(s) of the medicinal product for human use subject to the application, and to reference the articles in the 'peer review' journals for this purpose,

- Any claim that is unknown or inferred from the characteristics of the medicinal product for human use or treatment group in the summary of product characteristics should be discussed in the **(Amended:OG-24/9/2022-31963)** nonclinical/clinical overview/summaries and supported by published literature or additional studies,

- Where possible, the applicant provides additional evidence that the safety and efficacy properties of different salts, esters or derivatives of an active substance(s) which he claims are essentially similar to the existing active substance(s) are equivalent.

3. ADDITIONAL DATA REQUIRED IN SPECIFIC SITUATIONS

Where the active substance(s) of an essentially similar medicinal product for human use contains the same therapeutic effect as the original authorized product associated with a different salt/ester complex/derivative, evidence proving that there is no change in the pharmacokinetics, pharmacodynamics and/or in toxicity which lead to the modification of the safety/efficacy profile shall be demonstrated. In case of failure to present such evidence, this association shall be considered as a new active substance.

Where a medicinal product for human use is intended for a different therapeutic use or presented in a different pharmaceutical form or to be administered by different routes or in different doses or with a different posology, the results of appropriate toxicological and pharmacological tests and/or of clinical trials shall be provided.

4. BIOSIMILAR MEDICINAL PRODUCTS

For biological medicinal products, the requirements specified in subparagraph (c) of the first paragraph of Article 9 of this Regulation must be fulfilled. If the information required in the case of essentially similar products (bio-similar medical products) does not permit the demonstration of the similar nature of two biological medicinal products, additional data, in particular, the toxicological and clinical profile, shall be provided.

(Amended:OG-24/9/2022-31963) In case a marketing authorization application for a biological medicinal product is made after the expiry of the data protection period by a separate applicant for a biological medicinal product that references the reference medicinal product authorized in Türkiye and is defined in paragraph 3.2. of Part I of this Annex, the following shall apply:

- The information to be provided will not be limited to the information requested in Modules 1, 2 and 3 (pharmaceutical, chemical and biological data) and shall be supported by bioavailability and bioequivalence data. The type and amount of additional information (toxicological and other **(Amended:OG-24/9/2022-31963)** nonclinical and appropriate clinical data) shall be determined on a case-by-case basis in accordance with relevant scientific guidelines.

- Due to the diversity of biological medicinal products, the identified studies foreseen in Modules 4 and 5 shall be requested by the Agency taking into account the specific characteristics of each biological medicinal product.

The general principles to be applied are specified in the relevant guide, which takes into account the characteristics of the relevant biological medicinal product. If the authorized reference medicinal product has more than one indication, the efficacy and safety of the biological medicinal product claimed to be similar must be proven or, if necessary, demonstrated separately for each indication.

5. FIXED COMBINATION MEDICINAL PRODUCTS

Applications made based on subparagraphs (ç) and (d) of the first paragraph of Article 9 of this Regulation are valid for new medicinal products for human use consisting of at least two active substances, which were not previously authorized as fixed combination medicinal products for human use.

The complete dossier (Modules 1 to 5) shall be submitted for such fixed component medicinal product for human use applications. Where applicable, information on production sites and incidental substances and safety assessment shall be provided.

6. REQUIRED DOCUMENTS FOR MARKETING AUTHORIZATION APPLICATIONS IN EXCEPTIONAL SITUATIONS

As stated in Article 36 of this Regulation;

- The therapeutic indications for the medicinal product for human use are too rare to expect the applicant to provide comprehensive evidence, or

- Inability to provide detailed information in the light of available scientific data, or

- The Agency may grant marketing authorization to a medicinal product for human use subject to certain conditions, when the applicant proves objectively and verifiablely that it cannot provide comprehensive data on efficacy and safety under normal use conditions, due to the fact that collecting such information is contrary to the generally accepted medical ethical principles.

These obligations may include the following:

- The applicant will carry out the scheduled studies determined by the Agency within a certain period of time, the results of which will form the basis for the re-evaluation of the benefit/risk balance.

- The medicinal product for human use must be available only by prescription and, in certain cases, it must be administered under strict medical supervision, possibly in a hospital and by a person authorized for radiopharmaceuticals.

- Instructions for use and other medical information guides should be prepared in a way that draws the attention of medical personnel to the lack of some aspects of the properties of the medicinal product for human use.

7. MIXED MARKETING AUTHORIZATION APPLICATIONS

Mixed marketing authorization applications refer to registration application files, which are a combination of limited clinical or preclinical study reports made by the applicant in Module 4 or 5 of this Regulation, and contain bibliographic references. Other modules will follow the pattern outlined in Part I of this annex. The Agency accepts the form submitted by the applicant by evaluating it on a per-application basis.

PART III

PARTICULAR MEDICINAL PRODUCTS

This Chapter sets out the specific requirements regarding the nature of identified medicinal products for human use.

1. BIOLOGICAL MEDICINAL PRODUCTS

1.1. Plasma-Derived Medicinal Products For Human Use

For medicinal products for human use derived from human blood or plasma and by derogation from the provisions of Module 3, the dossier requirements mentioned in 'information related to the starting and raw materials', for starting materials obtained from human blood/plasma may be replaced by a Plasma Master File certified in accordance with this Part.

a) Principles

For the purposes of this Annex:

- They are stand-alone documents submitted separately from the PMF authorization dossier and are the information and documents containing detailed information about the sub/main fractions of a for human use medicinal product or the medical device specified in the Medical Device Regulation and the whole human plasma used as a starting material or raw material for the production of active substance(s) and excipient(s).

- Centers or institutions where human plasma is fractionated/processed maintain and update the information specified in the PMF.

- PMF is given to the Agency by the applicant or the marketing authorization holder. In cases where the PMF holder is different from the applicant or marketing authorization holder, the PMF must be given to the applicant or marketing authorization holder to be submitted to the Agency. In any case, the applicant or the marketing authorization holder assumes responsibility for the medicinal product for human use.

- While making a decision on the application for an imported product, the Agency seeks to have the certificate of the competent health authority of the country to be imported.

- For the marketing authorization application dossier of a medicinal product for human use containing a component derived from human plasma, reference is made to the PMF of the plasma used as the starting material/raw material.

b) Content

In particular, it contains the following information on plasma used as PMF starting material/raw material in accordance with the provisions of the relevant Regulation on testing of donors or donations:

I. Plasma origin

1.Information on centers or establishments in which blood/plasma collection is carried out, including inspection and approval and epidemiological data on blood transmissible infections,

2. Information on centers or establishments in which testing of donations and plasma pools is carried out, including inspection and approval status,

3. Selection/exclusion criteria for blood/plasma donors,

4. System in place which enables the path taken by each donation to be traced from the blood/plasma collection establishment through to finished products and vice versa.

II. Plasma quality and safety

1. Compliance with Pharmacopoeia monographs,

2. Testing of blood/plasma donations and pools for infectious agents, including information on test methods and, in the case of plasma pools, validation data on the tests used,

3. Technical characteristics of bags for blood and plasma collection, including information on anticoagulant solutions used,

4. Conditions of storage and transport of plasma,

5. Procedures for any inventory hold and/or quarantine period,

6. Definition of the plasma pool.

III. System that defines the conditions of interaction and accepted specifications between the place of manufacture or plasma fractionator/processor of medicinal products for human use derived from plasma and, on the other hand, blood plasma collection centers, testing centers or establishments.

In addition, the Plasma Master File contains a list of medicinal products for human use for which the Plasma Master File is valid, including clinical trial products covered by the Regulation on Clinical Trials of Medicines and Biological Products.

c) Evaluation and Certification

- For products that have not been authorized yet, the applicant submits a complete and complete dossier to the Agency, together with a separate PMF, if it is not already available to the Agency.

- The Agency evaluates PMF scientifically and technically.

- The PMF is updated annually by the applicant and the application for variation is evaluated and the applicant is notified of eligibility by the Agency.

- Changes to be made after the approval of the PMF are subject to the provisions of the Regulation on Changes in Medicinal Products for Human Use, which was published in the Official Gazette dated 23/5/2005 and numbered 25823.

- In line with the above-mentioned provisions, the Agency re-evaluates the related medicinal products for human use authorized on the basis of the PMF, taking into account the certification, re-certification and changes of the related PMF.

1.2. Vaccines

By derogation from the provisions of Module 3 on active substance(s) of vaccines, the following requirements shall apply when based on the use of a Vaccine Antigen Master File (VAMF) system:

The marketing authorization application dossier of a vaccine other than the human influenza vaccine shall be required to include a Vaccine Antigen Master File for every vaccine antigen that is an active substance of this vaccine.

a) Principles

For the purposes of this annex:

- VAMF refers to the document submitted separately from the marketing authorization application dossier, containing relevant information on the biological, pharmaceutical and chemical structure of each active substance that is a part of the medicinal product for human use. The stand-alone documentation may also be utilized by the same applicant or marketing authorization holder for one or more monovalent and/or combined vaccines.

- A vaccine may contain one or several distinct vaccine antigens. There are as many active substance(s) as vaccine antigen(s) present in a vaccine.

- A combined vaccine contains at least two distinct vaccine antigens aimed at preventing a single or several infectious diseases.

- A monovalent vaccine is a vaccine, which contains one vaccine antigen aimed at preventing a single infectious disease.

b) Content

The VAMF contains information from the relevant section of Module 3 (active substance) on 'Quality Data' referred to in Part I of this Annex:

Active Substance

1. General information, including information demonstrating compliance with the relevant monograph(s) of the Pharmacopoeia.

2. Information on the production of the active substance: this heading covers the production process, information on starting and raw materials, special precautions regarding TSEs, safety assessment of unexpected agents, and plant and equipment.

3. Characterization of the active substance.

4. Quality control of the active substance

5. Reference standard and materials

6. Container and closure system of the active substance

7. Stability of the active substance.

c) Evaluation and Certification

- For new vaccines containing a new vaccine antigen, the applicant submits to the Agency a complete and complete file with the VAMF of each vaccine antigen that is part of the new vaccine. The Agency evaluates each of the Vaccine Antigen Master File from a scientific and technical point of view.

- The provisions of the above paragraph apply to all vaccines consisting of a new combination of vaccine antigens, regardless of whether the vaccine antigens are part of currently authorized vaccines.

- Changes to be made after the approval of the Vaccine Antigen Master File are subject to the provisions of the Regulation on Changes in Medicinal Products for Human Use that have been Authorized or Application for Authorization has been made. The application for variation is evaluated and the applicant is notified of eligibility by the Agency.

- As the second step of the provisions specified in the first, second and third paragraphs above, the Agency approves the VAMF regarding the human medicinal product(s) for which the same Vaccine Antigen Master File is used and evaluates the variation applications regarding it.

2. Radiopharmaceuticals and precursors

2.1. Radio-pharmaceuticals

Within the scope of this section, a complete and complete dossier containing the following information is submitted for applications made in accordance with Article 5 and Article 8 of this Regulation, subparagraph (v) and related articles:

Module 3

a) In radiopharmaceutical kits that will be marked with radioactive substance after being procured from the production site, the part of the formulation intended to bind to or carry the radionuclide is considered as active substance(s). Descriptions of the production methods of radiopharmaceutical kits also include details on the manufacture of the kit and the proposed final processes to obtain the radioactive medicinal product. Required specifications of the radionuclide shall be defined in accordance with the general monograph or special monograph of the pharmacopoeia, where possible. In addition, any compounds essential for the radio-labelling shall also be described. The structure of the radio labelled compound shall also be defined.

For radio-nuclides, the nuclear reactions involved shall be discussed.

In the generator, both parent and daughter radionuclides shall be considered active substance(s).

b) Information on the nature of the radionuclide, the definition of the isotope, possible impurities, carrier, use and specific activity shall be provided.

c) Starting materials shall include irradiation materials.

ç) Opinions on chemical/radiochemical purity and its relation with biodistribution shall be provided.

d) Radionuclidic purity, radiochemical purity and specific activity shall be defined.

e) For generators, details of testing on parent and daughter radionuclides shall be provided. For generator-eluates, tests for mother radio-nuclides and for other constituents of the generator system shall be provided.

f) The requirement to express the content of active substance(s) in terms of the mass of active entities shall only apply to radio-pharmaceutical kits. For radio-nuclides, radioactivity shall be expressed in Becquerels at a given date and, if necessary, time with reference to time zone. The type of radiation shall be indicated.

g) For kits, the specifications of the finished product shall include tests on the performance of products after radio-labeling. Controls for the radiochemical and radionuclidic purity of the radiolabeled compound will be included. Any material essential for radio-labelling shall be identified and assayed.

ğ) Stability information shall be provided for radionuclide generators, kits and radioactively labeled products. Radiopharmaceuticals presented in multiple dose vials shall be documented stability during use.

Module 4

It is envisaged that toxicity may be associated with a radiation dose. In diagnosis, this is a consequence of the use of radio-pharmaceuticals; in therapy, it is the desired property. Therefore, assessments of the efficacy and safety of radiopharmaceuticals consider requirements for medicinal products and radiation dosimetry considerations. Organs/tissues exposed to radiation shall be documented. Absorbed radiation dose estimates shall be calculated according to a specified, internationally recognized system by a particular route of administration.

Module 5

Results of clinical trials shall be presented where applicable, otherwise justified in the clinical overview.

2.2. Radiopharmaceutical Precursors for Radioactive Labeling

In the specific case of a radio-pharmaceutical precursor intended solely for radio-labeling purposes, the primary objective shall be to present information that would address the possible consequences of poor radio-labeling efficiency or *in vivo* dissociation of the radio-labeled conjugate (eg., questions related to the effects produced in the patient by free radio-nuclide). In addition, it is also necessary to present relevant information relating to occupational hazards (eg., radiation exposure to hospital staff and to the environment).

In particular, the following information shall be provided where applicable:

Module 3

Where applicable, the provisions of Module 3 for the registration of radiopharmaceutical precursors Chapter III, 2.1. It is valid as stated in articles (a) and (ğ).

Module 4

Regarding single-dose and repeated-dose toxicity, the results of studies performed in accordance with the Principles of Good Laboratory Practices, Harmonization of Test Units, Regulation on Good Laboratory Practices and Inspection of Studies shall be provided and verified.

Mutagenicity studies on the radio-nuclide are not considered to be useful in this particular case. Information relating to the chemical toxicity and disposition of the relevant 'cold' nuclide shall be presented.

Module 5

Clinical information generated from clinical studies using the precursor itself is not considered to be relevant in the specific case of a radio-pharmaceutical precursor intended solely for radio-labeling purposes.

However, information demonstrating the clinical utility of the radiopharmaceutical precursor when attached to relevant carrier molecules shall be presented.

3. HERBAL MEDICINAL PRODUCTS

Applications for herbal medicinal products shall provide a full dossier in which the following specific details shall be included.

Module 3

The provisions of Module 3 also apply to the registration of herbal medicinal products, including compliance with the pharmacopoeial monograph(s). The state of scientific knowledge at the time when the application is lodged shall be taken into account.

The following aspects specific to herbal medicinal products shall be taken into account:

1. Herbal substances and herbal preparations:

The terms related to "herbal substances and preparations" in this annex shall be considered equivalent to the terms of "herbal medicines and herbal medicine preparations" specified in the pharmacopoeia.

With respect to the nomenclature of the herbal substance, the binomial scientific name of the plant (species, variety and author) and chemotype (where applicable), the parts of the plants, the definition of the herbal substance, the other names (synonyms mentioned in other Pharmacopoeias) and the laboratory code shall be provided.

With respect to the nomenclature of the herbal preparation, the binomial scientific name of plant (species, variety and author) and chemotype (where applicable), the parts of the plants, the definition of the herbal preparation, the ratio of the herbal substance to the herbal preparation, the extraction solvent(s), the other names (synonyms mentioned in other Pharmacopoeias) and the laboratory code shall be provided.

For the purpose of documenting the section of the structure for herbal substance(s) and herbal preparation(s) where applicable, the physical form, the description of the constituents with known therapeutic activity or markers (molecular formula, relative molecular mass, structural formula, including relative and absolute stereo-chemistry, the molecular formula and the relative molecular mass) as well as other constituent(s) shall be provided.

For the purpose of documenting the section on the manufacturing site of the herbal substance, the name, address and responsibility of each supplier (including toll manufacturing sites) and each proposed site or facility involved in production/collection and testing of the herbal substance shall be provided, where appropriate.

For the purpose of documenting the section on the manufacturing site of the herbal preparation, the name, address and responsibility of each manufacturer (including toll manufacturing site) and each proposed manufacturing site or facility involved in manufacturing and testing of the herbal preparation shall be provided, where appropriate.

For the purpose of describing the manufacturing process and process controls for the herbal substance, information shall be provided to adequately describe the plant production and plant collection. This information includes the geographical source of the herbal medicinal product and the conditions of sowing, harvesting, drying and storage.

For the purpose of describing the manufacturing process and process controls for the herbal preparation, the information shall be provided to adequately describe the manufacturing process of the herbal preparation. This information includes processing, solvents and reagents (reagents), purification steps and standardization.

With respect to the manufacturing process development, a brief summary describing the development of the herbal substance(s) and herbal preparation(s) where applicable shall be provided, taking into consideration the proposed route of administration and usage. Results comparing the phyto-chemical composition of the herbal substance(s) and herbal preparation(s) where applicable used in supporting bibliographic data and the herbal substance(s) and herbal preparation(s), where applicable, contained as active substance(s) in the herbal medicinal product applied for shall be discussed, where appropriate.

With respect to the elucidation of the structure and other characteristics of the herbal substance, information on the botanical, macroscopical, microscopical, phyto-chemical characterization and biological activity if necessary, shall be provided.

With respect to the elucidation of the structure and other characteristics of the herbal preparation, information on the phyto-chemical and physicochemical characterization and biological activity if necessary, shall be provided.

Specifications of herbal substance(s) and herbal preparation(s) shall be provided where applicable.

The analytical procedures used for testing the herbal substance(s) and herbal preparation(s) where applicable shall be provided.

With respect to the validation of analytical procedures, analytical validation information, including experimental data for the analytical procedures used for testing the herbal substance(s) and herbal preparations where applicable shall be provided.

With respect to batch analyses, description of batches and results of batch analyses for the herbal substance(s) and herbal preparation(s) where applicable shall be provided, including those for pharmacopoeia substances.

The specifications for the herbal substance(s) and herbal preparation(s) where applicable shall be provided.

Information on the reference standards or reference materials used for testing of the herbal substance(s) and herbal preparation(s) where applicable shall be provided.

Where the herbal substance or the herbal preparation is the subject of a monograph, the applicant can apply for a certificate of suitability that was granted by the European Directorate for the Quality of Medicines.

2. Herbal Medicinal Products

With respect to the formulation development, a brief summary describing the development of the herbal medicinal product should be provided, taking into consideration the proposed route of administration and usage. Results comparing the phyto-chemical composition of the products used in supporting bibliographic data and the herbal medicinal product applied for shall be discussed, where appropriate.

4. ALLERGEN PRODUCTS

Within the scope of this section, a complete and complete file containing all the information specified in the applications made pursuant to Article 5 and Article 8 of this Regulation and related articles is submitted.

General principles to be applied for allergen extracts from the allergen group that are in close structural relationship with each other are produced by the same manufacturer, the place of production of the finished product is the same, extraction and the reference allergen product, which is representatively selected among the products with the same production processes, and the allergen extracts from the allergen group that are closely related to each other, produced by the same manufacturer, with the same place of production of the finished product, extraction and the associated allergen product, which refers to a representative selected product among products whose manufacturing processes are exactly the same shall be stated in the guide published by the Agency regarding allergen products.