

Regulation on the Marketing Authorization of Medicinal Products for Human Use

SECTION ONE

Objective, Scope, Legal Basis and Definitions

Objective

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

Scope

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

However, this Regulation shall not apply to;

- a) Any product prepared in a pharmacy specifically for a patient in accordance with a prescription and commonly referred as the magistral formula,
- b) Any product prepared in a pharmacy in accordance with the formulas of a pharmacopoeia, intended to be supplied directly to patients served by the pharmacy in concern and commonly referred as the officinal formula,
- c) Medicinal products intended to be used in research and development studies, without prejudice to the provisions of the Regulation on Clinical Trials, published on the Official Gazette dated 29/01/1993, with no. 21480,
- d) Any semi finished products intended for further processing by an authorized manufacturer,
- e) Any radionuclides in the form of sealed sources,
- f) Whole blood, plasma or blood cells of human origin.

Legal basis

Article 3- This Regulation has been prepared on the basis of the Law no. 1262, dated 14/05/1928, on Pharmaceutical and Medicinal Preparations, article 3/k of the Fundamental Healthcare Law dated 07/05/1987, with no. 3359, (**Amended: OG-14/11/2013-28821**) article 6 of the Law dated 11/4/2007, with no. 5624 on Blood and Blood Products and article 27 of the Decree Law dated 11/10/2011 with no.663 on the Organisation and Duties of the Ministry of Health;

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

Definitions

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

- a) Ministry: The Ministry of Health,
- b) Law: The Law no. 1262 on Pharmaceutical and Medicinal Preparations,
- c) Medicinal Product for Human Use/Product: Any natural and/or synthetic origin active substance or combination of substances administered to human beings with a view to treating and/or preventing a disease, making a diagnosis, correcting or modifying a physiological function,

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

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

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

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

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

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

i) 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,

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

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

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

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

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

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

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

p) Granting Marketing authorization process: The examination and approval procedure carried out by the Ministry in order to put a medicinal product for human use to the market,

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

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

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

- t) TAEK: Turkish Atomic Energy Authority
- u) Specific Activity: Density of activity in a unit mass of a radioactive substance, defined as Curie or Becquerel,
- 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,
- v) Original Medicinal Product: Any product authorized/permitted to be introduced into the market for the first time in the world, upon proof of holding scientifically acceptable efficiency, quality and safety in terms of active substance(s),
- y) (**Amended: OG-14/11/2013-28821**) Generic Medicinal Product: A medicinal product having the same qualitative and quantitative composition and the same pharmaceutical form as the original medicinal product in terms of active ingredients and whose bioequivalence to the original medicinal product is shown by appropriate bioavailability studies (Different salts, esters, ethers, isomers, enantiomers, isomer combinations, complexes or derivatives of an active ingredient shall be deemed the same active ingredient unless they significantly differ in terms of their safety and/or efficacy characteristics. 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. Bioavailability studies need not be required of the applicant if he can demonstrate that the generic medicinal product meets the relevant criteria as defined in the appropriate detailed guidelines.)
- z) (**Appended: OG-22/4/2009-27208**) Manufacturing site: The site where the product is market released (batch release),
- aa) (**Appended: OG-22/4/2009-27208**) Co-marketed Product: A product that has the same qualitative and quantitative composition, the same pharmaceutical form, the same manufacturing site as and otherwise identical in all aspects, other than trade name, with the authorized product or the product for which an authorization application or co-application has been filed.

SECTION TWO

Marketing Authorization Application

Marketing authorization

Article 5- (**Amended: OG-22/4/2009-27208**)

No medicinal product for human use can be marketed unless authorized by the Ministry pursuant to this Regulation. The marketing authorization holder is obligated to notify the Ministry when the product is placed on the market. The Ministry shall notify the marketing authorization holder within 5 (five) days that such information is entered in record.

The authorization procedure shall equally apply to radionuclide generators, radionuclide kits, radionuclide precursors and industrially prepared radiopharmaceuticals.

Additional authorization is not required for positron-emitting radionuclides, used at a healthcare institution that is authorized to use radiopharmaceutical medicinal products by such institution or by a competent person therein having prepared it pursuant to manufacturer's instructions immediately before its administration to patients, as well as for radiopharmaceuticals derived from them and radiopharmaceuticals prepared of authorized radionuclide generators, radionuclide kits, radionuclide precursors, provided these are used at the healthcare institution producing them.

Furthermore, where the Ministry is presented with appropriate literatures showing that the efficacy and safety of a product, unauthorized in Turkey, is proven abroad or in Turkey and that it has come into routine use, an authorization shall not be required of magistrally prepared

radiopharmaceuticals to the extent that their use shall be limited to the healthcare institutions where these are used.

Application

Article 6- Real persons or legal entities located within the boundaries of Turkey shall prepare and submit to the Ministry, all particulars and documents required for obtaining a marketing authorization of a product and to be submitted at the marketing authorization application specified in Annex-I of this regulation, in accordance with the format envisaged in the referred regulation for each pharmaceutical form.

Persons eligible to apply for marketing authorization

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

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

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

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

Particulars and documents to be submitted at the application

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

a) (**Amended: OG.31/7/2009-27305**) Diploma or its approved copy by the Ministry showing that applicant may practice one of the professions specified in article 7 of this Regulation,

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

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

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

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

f) Name of the product,

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

h) Description of the manufacturing method,

i) Therapeutic indications, contraindications and adverse reactions,

i) Strength, pharmaceutical form, method and route of administration, shelf life and amount in package,

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

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

22/4/2009-27208) Where deemed appropriate by the Ministry, some of these analyses, tests and controls, specified on product basis, may be omitted, provided doing so does not affect security, safety and quality.

l) Results of physico-chemical or microbiological tests,

m) Toxicological and pharmacological tests and clinical trials,

n) (**Amended: OG-22/4/2009-27208**) Where a product authorized abroad is imported or is manufactured on license, the original copies of summary of product characteristics (SPC), the patient information leaflet and packaging samples, along with their translations, for the submitted product, whose up-to-dateness is warranted by the applicant,

o) (**Amended: OG-22/4/2009-27208**) 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, registering and selling the subject product in Turkey, and in the case of co-marketing, a document issued by the licensor showing that a real person or legal entity other than the sole authorized representative in Turkey is also granted co-marketing authorization, along with a Turkish translation thereof, and the written consents issued by the real persons or legal entities with regard to the co-marketing arrangement between such real persons or legal entities to undertake such co-marketing activity.”

ö) (**Amended: OG-22/4/2009-27208**) 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 a real person or legal entity, if any, other than the sole authorized representative in Turkey is also granted co-marketing authorization along with its Turkish translation, and the written consents issued by the real persons or legal entities with regard to the co-marketing arrangement between such real persons or legal entities to undertake such co-marketing activity.

p) (**Amended: OG-22/4/2009-27208**) In the case of co-marketing of a product manufactured or planned to be manufactured in Turkey the written consents issued by the real persons or legal entities with regard to the co-marketing arrangement between such real persons or legal entities to undertake such co-marketing activity.

r) (**Amended: OG-22/4/2009-27208**) The GMP certificate, issued to the manufacturer by the Ministry or by an internationally recognized institution and approved by competent authorities of the appropriate country, indicating that the manufacturer is capable to carry out manufacturing operations in line with Good Manufacturing Practices; in the case of a product to be manufactured in Turkey and where the applicant is not the manufacturer, the notarized contract manufacturing agreement executed with a manufacturer that satisfies the requirements specified in the Regulation on Manufacturing Sites of Medicinal Products for Human Use, published in Official Journal #25268 of 23.10.2003.

s) (**Amended: OG-22/4/2009-27208**) In the case of a product that is imported or manufactured on license for which an application is pending, the other country or list of other countries where an authorization application for the product is pending (In such applications, it is required to submit a copy of the authorization certificate approved by health authorities from any of the listed countries before authorization is granted in Turkey).

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

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

ü) (**Amended: OG-22/4/2009-27208**) The summary of product characteristics specified in the packaging and labelling regulations and the patient information leaflet prepared accordingly, the internal and external packaging specimens in the dimensions and a design that are identical to the market release dimensions and design for the product, and in the case of products authorized abroad and imported/manufactured on license, the originals of summary of product characteristics, patient information leaflet from other countries along with their Turkish or English translations, which are declared to have been recently updated.

v) 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 authorized name of the country in question, the date of the transactions conducted and the relevant justification of such transaction.

y) (**Appended: OG-22/4/2009-27208**) In the context of pharmacovigilance practices, the résumé, address, telephone and fax numbers and tasking order of the person responsible for product safety.

z) (**Appended: OG-22/4/2009-27208**) In the context of the regulation on promoting medicinal products for human use, the document defining the scientific service and its address, telephone and fax numbers.

aa) (**Appended: OG-22/4/2009-27208**) In the case of an application for a co-marketed product, the written consents issued by the real persons or legal entities with regard to the co-marketing arrangement between such natural or juristic persons to undertake such co-marketing activity and the Module 1 data, only.

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

Abridged application

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

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

1) The medicinal product shall be (**Amended: OG-22/4/2009-27208**) basically similar to a medicinal product which previously authorized in Turkey and the marketing authorization holder of the original medicinal product shall have consented to the use of the toxicological, pharmacological and/or clinical references contained in the dossier of the original medicinal product for the purpose of evaluating the referred application,

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

3) (**Amended: OG-11/06/2005-25842**) Where the medicinal product is essentially similar to a medicinal product which has been authorized in accordance with the current legislative provisions and has completed its data exclusivity period. In the implementation of this subclause, data exclusivity shall apply in terms of the original products for which no generic marketing authorization application has been submitted in Turkey until 1/1/2005 among the original products which have been authorized for the first time in one of the countries within the Customs Union Area after 1/1/2001 as well as original products which shall be authorized

for the first time in one of the countries within the Customs Union Area after 1/1/2005; the data exclusivity period shall consist of 6 (six) years to commence as of their first marketing authorization date 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 6 (six) years shall be limited to this patent period.

(Amended second paragraph: OG-22/4/2009-27208) All applications having the nature of a variety and of an application for an additional dose, pharmaceutical form, route of administration and presentation, and applications for authorization of combinations, containing known constituents, where each such constituent has a medical use as established with a reasonable level of effectiveness and acceptable level of safety, but do not include a new indication other than its known therapeutic indications even where a clinical trial is performed for each constituent, shall be considered a part of the initial authorization, except in the circumstances specified in subparagraph (b) hereof. Where up-to-date scientific data and/or bibliographic references basing on published data are submitted for each such constituent, the authorization application for a combination preparation shall be made pursuant to Annex 1. Where such a combination is conceived on an existing authorization application, a Type II variation application shall suffice.

b) **(Amended first paragraph:OG-22/4/2009-27208)** Clinical trial results must be submitted for a new medicinal product, which contains known constituents, which do not individually have a medical use established with reasonable efficacy and acceptably safety, but in its combined form, offers a therapeutic use different from the known therapeutic uses of each of its constituents. However, references relating to each constituent do not need to be submitted. A new authorization application must be filed for such combinations.

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

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

Granting marketing authorization in special cases

Article 10- In below mentioned special cases, marketing authorization may be granted within the framework of the decision of the Ministry, provided that more advanced studies are conducted in consequence pursuant to the granting of marketing authorization and the communication of the adverse effects pertaining to the medicinal product:

- a) The therapeutic indications pertaining to the relevant product are not sufficient to enable the applicant to provide detailed evidence,
- b) Detailed information may not be provided in the light of the current scientific data,
- c) The collection of such data results to be in violation of the accepted ethical norms.

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

Summary of Product Characteristics

Article 11- (Amended: OG-22/4/2009-27208)

The summary of product characteristics must be submitted pursuant to the guidance which shall be issued on basis of this Regulation, and must include data on pharmaceutical, clinical and pharmacological characteristics of the medicinal product for human use as well as details regarding the party applying for authorization.

Expert reports

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

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

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

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

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

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

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

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

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

SECTION THREE

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

Preliminary examination of the application

Article 13- (Amendment first sentence:OG-22/4/2009-27208) The summary of product characteristics must be submitted pursuant to the guidance which shall be issued on basis of this Regulation, and must include data on pharmaceutical, clinical and pharmacological characteristics of the medicinal product for human use as well as details regarding the party applying for authorization. Relevant evaluation shall be conducted within 30 (thirty) days as of the receipt of the application dossier by the Ministry and the result will be communicated to the applicant. In case of deficiencies in the application dossier, the applicant shall complete these within 30 (thirty) days. The second preliminary analysis to be conducted upon the remedy of the deficiencies and submittal to the Ministry, shall be finalised within 30 (thirty) days.

Refusal of the application on procedural grounds

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

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

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

Period of marketing authorization process

Article 15- The Ministry shall analyse the marketing authorization application which has undergone a preliminary analysis and results to be complete, for checking whether the marketing authorization conditions have been fulfilled and shall finalise the process within 210 (two hundred and ten) days after the acceptance of the application. (Amendment second

sentence: OG-22/4/2009-27208) However, the aforesaid period shall not include extraordinary circumstances and the period of time throughout which the applicant procures the documents that the Ministry required of it.

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

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

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

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

(Appended third paragraph: OG-22/4/2009-27208) In the case of an application that is original in treatment or diagnosis, is novel or is needed from a public health perspective to reduce state's healthcare expenditures and to ensure rapid public access to the drug, or an application filed pursuant to Article 9 or 10, the authorization procedure shall be completed within no more than 180 days. The holdup provisions equally apply.

(Appended fourth paragraph: OG-22/4/2009-27208) In the case of an authorization application for a co-marketed product where the reference product is unauthorized but has an application pending, both dossiers shall be processed in parallel. Where the reference product is authorized in Turkey, the Ministry shall examine solely the Module 1 (Administrative data), and conclude the application within 90 days, provided no incompleteness exists.

(Appended fifth paragraph: OG-14/11/2013-28821) In cases where document and particular deficiencies requested by the Ministry in accordance with this article, are not completed in a year or the applicant does not perform any transaction, the dossier shall be removed from the process and returned.

Marketing authorization criteria

Article 16- Criteria to be taken into account by the Ministry while granting marketing authorization for medicinal product for human use are as follows:

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

b) Have proven reliability,

c) **(Repealed:OG-22/4/2009-27208)**

d) Have the adequate technical and pharmaceutical properties.

(Appended second paragraph: OG-22/4/2009-27208) Where public health warrants it, the Ministry may, taking into consideration pharmacoeconomic data, waive some of the above criteria.

Evaluation of applications

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

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

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

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

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

Refusal of the application on fundamental grounds

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

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

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

c) **(Repealed: OG-22/4/2009-27208)**

d) **(Repealed: OG-22/4/2009-27208)**

e) **(Amended: OG-14/4/2011-27905)** The qualitative and quantitative formula conformity and declared specifications are out of acceptable limits although the analysis steps specified in the second paragraph have been completed,

(2) **(Appended: OG-14/4/2011-27905)** The product is analyzed using the reported control methods. In case of any non-conformity in the first analysis, the analysis is repeated by requesting the corrected sample from the company. In the second analysis, in case of nonconformity, an evaluation meeting is held with the representatives of the company about the analysis method and the analysis method of the new sample is determined and the analysis is performed. In the third analysis, if there is any nonconformity, a final evaluation meeting is held with the representatives of the company, the nonconformity of the analysis is described and the new analysis method is determined and the analysis is conducted for the last time.

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

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

The objection submitted shall be evaluated by the Ministry within 90 (ninety) days and the result will be communicated to the applicant. During the evaluation of the objection, the applicant will be granted the right for oral explanation and defense, where necessary. **(Amended last sentence: OG-22/4/2009-27208)** The decision adopted with respect to an objection cannot be challenged unless new data and documents can be produced which can potentially affect the decision.

Granting marketing authorization

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

A second local or import marketing authorization shall not be granted for any product with the same formulation and pharmaceutical form, already authorized by the Ministry, to the same real person or legal entity, even if the product has a different commercial name.

The names of products for which a marketing authorization is granted by the Ministry, shall be declared on the Official Gazette with the name and surname of the marketing authorization holder and with the marketing authorization number.

Validity period of marketing authorizations

Article 21- (Amended: OG-22/4/2009-27208)

By no later than 3 (three) months before the end of 5th (fifth) year after the grant of authorization, the authorizations shall be presented to the Ministry with necessary

pharmacovigilance data as well as the data on quality, safety and efficacy, reflecting all changes that occurred since the grant of authorization.

The authorization dossiers of products that were authorized before the effectiveness of this Regulation may be reissued pursuant to Annex 1 of this Regulation.

Suspension of marketing authorization

Article 22- In the event of the detection of the following in a authorized product, the marketing authorization pertaining to the product shall be suspended by the Ministry:

- a) The emergence of the harmful effects in normal conditions of use,
- b) Detection of the lack of or insufficient therapeutic effect,
- c) Manufacturing with a formulation other than the formulation taken as basis in the marketing authorization,
- d) Performing variations not informed to and/or not approved by the Ministry, in the formulation, strength, pharmaceutical form, package and summary of product characteristics taken as basis in the authorization,
- e) Failure of the applicant to take into consideration the scientific and technical advancements in terms of the manufacture and control methods and the failure to perform any variation that may be required for the manufacture and control of the medicinal product according to generally accepted scientific methods and to present them to the approval of the Ministry,
- f) Failure to take into consideration any warning made with regard to the products determined to be defective as a consequence of the market controls conducted and the continuation of defective manufacture,
- g) Failure to comply with the relevant legislative provisions pertaining to the package and labelling and non-consideration of the warning made to the marketing authorization holder,
- h) No response provided by the marketing authorization holder to the instructions and warnings of the Ministry on the product,
- i) Detection of errors in the particulars and documents presented for the marketing authorization of a product in accordance with the provisions of this Regulation,
- j) (**Amended: OG-14/11/2013-28821**) Failure to actually place a medicinal product on the market within the first 3 (three) years after granting marketing authorization, or the absence of a authorized product that was previously introduced to the market for an uninterrupted year,
- k) (**Amended: OG-22/4/2009-27208**) The Ministry finding the justifications submitted by the firm acceptable,
- l) Decision to suspend the marketing authorization in consequence to the risk/benefit evaluation conducted by the Ministry with regard to the notifications received within the framework of the pharmacovigilance implementations.
- m) (**Additional article: OG-31/8/2019-30874**) Failure to notify transactions which are mandatory such as manufacturing, import, export, sale, return, disposal and recall of human medicinal products to the pharmaceutical track and trace system in accordance with procedures and principles set by the Ministry.

The manufacture (**Appended: OG-22/4/2009-27208**) or importation of a product the marketing authorization of which is suspended, shall be halted. The decision to be taken with regard to the products in distribution and sale shall be taken by the Ministry, upon consideration of the justification for suspending the marketing authorization.

Cancel of marketing authorization

Article 23- (**Amended: OG-14/11/2013-28821**)

The marketing authorization granted for the product shall be cancelled where the particulars and documents proving the contrary of the justification for suspension pertaining to products the marketing authorization of which has been suspended due to one or more

conditions specified in article 22 of this Regulation, are not presented latest within 6 (six) months, by the marketing authorization holder.

Upon marketing authorization holder's request, the marketing authorization issued for the product shall be suspended and announced on the Agency's website for one year. If there is not any transfer occurs, the marketing authorization shall be cancelled.

Manufacturing or importation of a product of which marketing authorization is cancelled shall be halted. The decision pertaining to the products in distribution and sale shall be taken by the Ministry, upon consideration of the justification for the revocation of the marketing authorization.

The names of products the marketing authorizations of which have been cancelled by the Ministry, shall be declared on the Official Gazette, with the name, surname of the marketing authorization holder and the relevant marketing authorization numbers.

Responsibility of the marketing authorization holder

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

- a) Manufacturing the product in compliance with the specifications presented in the annex of the application and accepted by the Ministry,
- b) Considering the scientific and technical progress in terms of manufacture and control methods and the presentation to the approval of the Ministry any amendment to enable the manufacture and control of the medicinal product with the generally accepted scientific methods,
- c) Updating, when necessary, summary of product characteristics and patient leaflet for the purpose of enabling a correct and safe use of the product,
- d) In the event of any variation pertaining to the product, communicating the variations to the Ministry within the framework of the pertinent guideline provisions,
- e) Providing response to the topics requested by the Ministry, in relation with the product,
- f) Fulfilling the obligations within the framework of pharmacovigilance implementations, in consequence to the market introduction of the product,
- g) Ensuring the procurement of measures for the purpose of preventing the contamination of infections in case of a biological product,
- h) Securing the market availability of the product of which he/she holds the marketing authorization,
- i) Forthwith communication with all relevant justifications, to the Ministry, of all measures taken for the purpose of suspending the marketing authorization of a product or withdrawing it from the market, due to its efficiency or for safeguarding public health,
- i) Fulfilling the requirements of the legislation pertaining to the product,
- j) Paying specified dues and fees pertaining the products.

Change of marketing authorization holder

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

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

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

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

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

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

1) (**Amended: OG-3/4/2012-28253**) Diploma copy approved by the Agency indicating that he/she is a member of the profession specified in article 7 of this Regulation, for the persons that may apply for marketing authorization,

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

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

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

c) The name, surname, address, telephone and fax numbers of the person receiving the marketing authorization with the change of marketing authorization holder, (**Appended: OG-22/4/2009-27208**) the updated summary of product characteristics, instructions for use, a sample each from the immediate and outer packages, and in case of transfers conducted via a notary-public, the original marketing authorization previously issued for the product in question.

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

(Amended third paragraph: OG-22/4/2009-27208) Where an original firm desires to change the real person or legal entity which it authorized for authorizing or selling the subject product in Turkey, upon the submission of the currently dated original document indicating the grant of power by the original firm for marketing authorization and sale of the product in Turkey, its notarized translation into Turkish, a letter from the current authorization holder that it returned the original authorization certificate or a court decision to the effect that the original authorization holder is no longer authorized, all requirements stipulated under this article as well as in the full and updated current product dossier approved by the Ministry, excluding paragraph one, subparagraph (a) of this Article, must be fulfilled.

(Amended fourth paragraph: OG-22/4/2009-27208) In the case of transfers through a notary office, where, in addition to the documents specified in subparagraphs (a), (b) and (c) of the first paragraph of this article,

a) a letter of commitment issued by the transferee to the effect that the product was not modified in any way during the application for transfer,

b) a letter of commitment issued by the transferee to the effect that all modifications and updates required by the Ministry relating to the product shall be performed after the transfer

are submitted fully and without any incompleteness, all updates required by the Ministry on the current product dossier and all actions to rectify any incompleteness shall be performed pursuant to appropriate guidelines following completion of the formalities for changing the product's authorization holder.

(Amended fifth paragraph:OG-22/4/2009-27208) In the case of transfers effected pursuant to fourth paragraph of this article, the Ministry shall conclude the application for change of authorization holder, made without any incompleteness as to the required data or documents, within 30 (thirty) days.

(Appended sixth paragraph:OG-22/4/2009-27208) 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 hereunder must be fulfilled.

Obtaining sales permit

Article 26- (Repealed:OG-22/4/2009-27208)

Variations pertaining to the marketing authorization

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

SECTION FOUR

Miscellaneous and Final Provisions

Confidentiality

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

Penalty provisions

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

Repealed legislation

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

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

With regard to the abridged applications presented in accordance with article 9 of this Regulation of which all provisions except for article 9 shall be enforced on **(Amended: OG-28/06/2005-25859)** 30/12/2005, the applications submitted in compliance with the application format indicated in the Regulation in force shall be accepted.

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

Temporary Article 3- For the conduct of the relevant evaluations with regard to the vaccines, antisera and allergen containing biological products introduced into the market with import permit, persons holding the import permit shall apply for marketing authorization

with the documents requested by the Ministry, **(Amended: OG-13/01/2007-26402)**⁽¹⁾ within 2 (two) years of the enforcement date of this Regulation. The import permits of products for which no marketing authorization application is submitted within this period shall not be valid.

Temporary Article 4- For the purpose of conducting the relevant evaluations pertaining to the products registered before the enforcement date of this Regulation, in accordance with the Regulation on Radiopharmaceuticals, published on the Official Gazette dated 23/12/1993, with no. 21797, the persons holding the certificate of marketing authorization shall apply for marketing authorization with the documents requested by the Ministry, **(Amended: OG-13/01/2007-26402)**⁽¹⁾ within 2 (two) years of the enforcement date of this Regulation. The certificates of marketing authorization pertaining to products for which no marketing authorization application is submitted within this period shall not be valid.

Enforcement

Article 31- Article 9 and the second paragraph of Temporary Article 1 of this Regulation shall be enforced as of 01/01/2005, as of the publication date, whereas the other provisions shall be enforced as of **(Amended: OG-28/06/2005-25859)** 30/12/2005.

Execution

Article 32- **(Amended: OG-14/11/2013-28821)** The provisions of this Regulation shall be executed by the President of Turkish Medicines and Medical Devices Agency.

⁽¹⁾ *The amendments made to the Regulation published in the Official Gazette dated 13/01/2007 and numbered 26402 shall enter into force on the date of publication with effect from 30/12/2006.*

Annex-I

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

Introduction and general principles

(1) The particulars and documents accompanying an application for marketing authorization pursuant to the provisions of this Regulation, shall be presented to the Ministry in accordance with the requirements set out in this Annex and shall follow the guidelines published by the Ministry regarding the Common Technical Document (CTD). Pursuant to the enforcement of the Common Technical Document to be published by the Ministry as guidelines, applications shall be submitted in accordance with the referred guidelines.

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

Module 1 Administrative Data

Module 2 Quality Information, Non-clinical and Clinical Summaries

Module 3 Chemical, Pharmaceutical and Biological Information

Module 4 Non-clinical Reports

Module 5 Clinical Study Reports

(3) The presentation of CTD to the Ministry is applicable for all types of marketing authorization applications irrespective of whether they are based on a full or abridged application. It is also applicable for all types of products including new chemical entities (NCE), radio-pharmaceuticals, plasma derivatives, vaccines, herbal medicinal products, etc.

(4) In assembling the dossier for application for marketing authorization, applicants shall also take into account the other legislation published by the Ministry, 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 sections of the European Pharmacopoeia are applicable. The manufacturing process shall comply with the requirements of the “Regulation Regarding the Manufacturing Sites of Medicinal Products for Human Use”, published on the Official Gazette dated 23/10/2003, with no. 25268 and with the principles set forth in the guidelines prepared on the basis of this Regulation.

(6) 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 pharmacotoxicological or clinical test or trial relating to the medicinal product and/or completed trials concerning therapeutic indications not covered by the application.

(7) All clinical trials conducted in Turkey, must fully comply with the requirements of the “Regulation on Clinical Trials”, published on the Official Gazette dated 29/01/1993, with no. 21480. During the assessment of an application, clinical trials, conducted outside Turkey, which relate to medicinal products 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.

(8) Non-clinical (pharmaco-toxicological) studies shall be carried out in conformity with the provisions specified in the “Regulation Regarding Good Laboratory Practice Principles and the Documentation of Test Laboratories” published on the Official Gazette dated 25/06/2002, with no. 24796 and in the “Regulation Regarding the Inspection of Good Laboratory Practice and the Control of the Studies”, published on the Official Gazette bearing the same date and number.

(9) All tests conducted on animals for experimental and other scientific purposes, shall be carried out in accordance with the relevant legal arrangements, for ensuring the protection of animals.

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

This Annex has been divided into four different parts:

Section 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).

Section II comprises ‘Specific applications’, i.e. well-established medicinal use, essentially similar products, fixed combinations, similar biological products, exceptional circumstances and mixed applications (bibliographic part and the part comprising own studies).

Section III deals with ‘Particular application requirements’ for biological medicinal products (Plasma Master File; Vaccine Antigen Master File), radio-pharmaceuticals, herbal medicinal products and orphan medicinal products.

Section IV deals with ‘Advanced therapy medicinal products’ and concerns specific requirements for gene therapy medicinal products (using human autologous or allogeneic system, or xenogeneic system) and cell therapy medicinal products both of human or animal origin and xenogeneic transplantation medicinal products.

SECTION I

DOSSIER REQUIREMENTS FOR STANDARDISED MARKETING AUTHORIZATION APPLICATIONS

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 copy approved by the Agency (**Amended phrase:OG-3/4/2012-28253**) pertaining to the professions specified in Article 7 of this implementing regulation; the certified document indicating that the applicant is authorized to submit an application; in the event of the applicant being a legal person, the original newspaper indicating the commercial

marketing authorization, which comprises the objectives of establishment of the company, partners, if any and the duties and titles of the responsible persons.

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, dosage 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 manufacturers of the finished product and the manufacturers of the active substance(s) and in the event of importation, the name and address of the importer.

The applicant shall identify the type of application and indicate what samples, if any, are also provided.

Annexed to the administrative data shall be copies of the marketing authorization /permit of the manufacturing site, as defined in the “Regulation Regarding the Manufacturing Sites of Medicinal Products for Human Use”, published on the Official Gazette dated 23/10/2004, no. 25268 and with regard to the product for which a marketing authorization has been submitted, together with a list of countries in which an application has been submitted, copies of certified product certificates granted by the other country or countries where the product has been introduced into the market and the summaries of product characteristics.

As outlined in the application form, the applicants shall provide, details of the medicinal product subject of the application, the proposed marketing authorization holder and manufactures, information on orphan medicinal product status or 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 11 of this Regulation.

1.3.2. Packaging and package leaflet

A proposed text for immediate and outer packaging as well as for the package leaflet shall be provided. All of these shall comply with all provisions pertaining to labelling and package leaflet of products, set forth in the relevant legislation.

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 concerned.

1.4. Information Regarding the Experts

In accordance with Article 12 of the Regulation, the experts must provide detailed reports of their observations pertaining to particulars and documents which constitute the marketing authorization dossier and in particular on Modules 3, 4 and 5 (chemical, pharmaceutical and biological documentation, non-clinical documentation and clinical documentation, respectively). The experts are required to address the critical points related to the quality of the medicinal product and of the investigations carried out on animals and human beings and bring out all the data relevant for evaluation.

These requirements shall be fulfilled upon providing a quality overall summary, a non-clinical overview (data from studies carried out in animals) and a clinical overview that shall be located in Module 2 of the marketing authorization 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 adequate technical and 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 Section II of the present Annex.

1.6. Environmental Risk Assessment

Where applicable, marketing authorization applications shall include a risk assessment overview document evaluating potential environmental risks to arise in consequence to the use and/or disposal of the medicinal product and make proposals for appropriate labelling provisions.

Environmental risk associated with the disposal of medicinal products containing or consisting of GMOs (Genetically Modified Organisms) shall be assessed within the framework of the relevant legislation of the Ministry of Agriculture.

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 any guidelines published in relation to this legislation, shall be taken into consideration during the submission of the documents.

The information shall consist of:

- an 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, as well as any additional information on the GMOs or the product of relevance to the assessment of the environmental risk;
- an environmental risk assessment report prepared on the basis of the information specified in the relevant legislation;
- Upon consideration of the abovementioned information and the Environmental Risk Assessment Report, final report which proposes a risk management plan including the information required to appear on the post-marketing surveillance plan, summary of product characteristics, labeling and package leaflets of relevant products containing GMOs,
- appropriate measures in order to inform the public.

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

2. MODULE 2: SUMMARIES

This Module aims to summarize the chemical, pharmaceutical and biological data, non-clinical data and the clinical data presented in Modules 3, 4 and 5 of the marketing authorization dossier and to provide the reports/overviews.

Critical points shall be addressed and analyzed. Summaries based on concrete data shall be presented in tabular form. Summaries presented in tabular form and other information shall provide cross-references to the main documentation presented in Module 3 (chemical, pharmaceutical and biological documentation), Module 4 (non-clinical documentation) and Module 5 (clinical documentation).

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

2.1. Comprehensive 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 which a marketing authorization 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. Non-clinical Overview

Studies conducted on animals in relation with the medicinal product and/or non-clinical in vitro evaluations shall be analyzed in an integrated and critical manner. In the event of deviation from the testing strategy and the relevant guidelines, the justifications and the discussions pertaining to such implementations shall be presented.

Except for biological medicinal products, an assessment of the potential pharmacological and toxicological impacts of impurities and degradation products shall be added. Current differences in the chirality, chemical form and impurity profile between the compound used in the non-clinical studies and the product to be marketed shall be discussed.

For biological medicinal products, comparability of materials used in non-clinical studies, clinical studies and the medicinal product to be marketed shall be discussed.

Any novel excipient shall be subjected to a specific safety assessment.

The characteristics of the medicinal product, as demonstrated by the results of non-clinical studies shall be defined and the results of the findings obtained on the safety of the medicinal product shall be discussed in terms of the intended clinical use in humans.

2.5. Clinical Overview

This section is intended to provide a critical analysis of the clinical data included in the clinical summary and Module 5. Thus, the approach to the clinical trial of the medicinal product, including the critical trial design, decisions and assessments pertaining to the investigations 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. It shall be necessary to submit a view on how efficacy and safety findings will support the proposed dosage and target indications and the evaluations about how the summary of product characteristics will be and how other approaches will optimize the benefits and manage the risks.

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

2.6. Non-clinical Summary

The results of the studies conducted on animals and pharmacology, pharmacokinetic and toxicology studies carried out in vitro shall be provided as factual written and tabulated summaries which will be presented in the following order:

- Introduction
- Pharmacological summary
- Pharmacological tabulated summary
- Pharmacokinetic summary
- Pharmacokinetic tabulated summary
- Toxicological summary
- Toxicological tabulated summary

2.7. Clinical Summary

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

Summarized clinical studies shall be presented in the following order:

- Summary of biopharmaceutical 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 CONTAINING CHEMICAL AND/OR BIOLOGICAL ACTIVE SUBSTANCES

3.1. Format and Presentation

The general outline of Module 3 shall be as follows

A) TABLE OF CONTENTS

B) BODY OF DATA

1) Active substance

a) General Information

- Nomenclature
- Structure
- General Properties

b) Manufacture

- Manufacturers
- Description of manufacturing process and process controls
- Control of materials
- Controls of critical phases and intermediates
- Process validation and/or evaluation
- Manufacturing process development

c) Properties

- Description of structure and other properties
- Impurities

d) Control of active substances

- Specifications
- Analytical procedures
- Validation of analytical procedures
- Batch Analyses
- Justification of specifications

e) Reference Standards or Materials

f) Primary Package (Container and Closure) System

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

2) Finished Medicinal Product

a) Description and composition of the medicinal product

b) Pharmaceutical development

- Components of the medicinal product
- Active substance

- Excipients
- Medicinal Product
- Formulation development
- Overages
- Physicochemical and Biological Properties
- Manufacturing process development
- Container closure system
- Microbiological attributes
- Compatibility

c) Manufacture

- Manufacturer(s)
- Batch formula
- Description of manufacturing process and process controls
- Controls of critical phases and intermediates
- Process validation and/or evaluation

d) Control of excipient(s)

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

e) Control of finished medicinal product

- Specification(s)
- Analytical Procedures
- Validation of analytical procedures
- Batch analyses
- Characterization of impurities
- Justification of specification(s)

f) Reference Standards or Materials

g) Primary Package (Container and Closure) System

h) Stability (in line with the guidelines on stability tests)

3) Appendices

- Facilities and equipment (biological medicinal products only)
- Adventitious agents safety evaluation
- Excipients

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)
- Presence of use of human and/or animal original materials in the manufacturing phases of medicinal products for human use (TSE/BSE certificate)

C) LITERATURE REFERENCES

3.2. Content: Basic principles and Requirements

All of the information pertaining to the chemical, pharmaceutical and biological data required to be provided shall be provided in relation with the active substance(s) and finished product, shall comply with following: The development, the manufacturing process, the characterization 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.

Two main sets of information shall be provided, dealing with the active substance(s) and the finished medicinal product, respectively.

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

Upon the request of the Ministry, all procedures implemented in the manufacture and control of finished medicinal product and the active substances, shall be described in detail to enable the repetition of in control tests. 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 European Pharmacopoeia, this shall be added to the monograph(s) and general section(s) by an appropriate detailed reference.

The monographs of the European Pharmacopoeia shall be applicable to all substances, preparations and pharmaceutical forms appearing in the monographs. In respect of other substances, compliance with national pharmacopoeia shall be required.

However, where a material in the European Pharmacopoeia or in the national 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 European Pharmacopoeia monograph or in the national pharmacopoeia might be insufficient to ensure the quality of the substance, the Ministry may request more appropriate specifications from the marketing authorization holder. The Ministry shall inform the authorities responsible for the pharmacopoeia in question. The marketing authorization holder shall provide the authorities of that pharmacopoeia with the details of the alleged insufficiency and the additional specifications applied.

In the case of analytical methods included in the European Pharmacopoeia, this description shall be replaced in each relevant section by the appropriate detailed reference to the monograph(s) and general section(s).

In case where starting and raw materials, active substances or excipients are described neither in the European Pharmacopoeia nor in the National 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 materials or excipients are the subject of a monograph of the European Pharmacopoeia, the applicant may apply for a certificate of suitability that granted by the European Directorate for the Quality of Medicines (EDQM) and present it in accordance with the relevant section of this Module.

The certificates of suitability to the monograph of the European Pharmacopoeia shall be regarded as replacement of the sections defined 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 European Directorate for the Quality of Medicines.

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 Ministry by the manufacturer of the active substance as an Active Substance Master File.

In case the manufacturer provides all relevant data to the applicant, the latter may be required to assume full 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. Particulars and documents supporting the application for such a modification shall be supplied to the Ministry; the particulars and documents pertaining to the open active substance section of the active substance master file shall also be submitted to the applicant.

With regard to the specific measures concerning the prevention of the transmission of animal spongiform encephalopathies, at each step of the manufacture, the applicant must demonstrate the compliance of the materials used with the legislation on minimizing the risk of transmitting animal spongiform encephalopathy agents (BSE/TSE) via medicinal products. Demonstration of compliance with the relevant legislation can be done by submitting either a certificate of suitability to the relevant monograph of the European Pharmacopoeia or by the supply of scientific data to substantiate this compliance, to the Ministry.

With regard to adventitious agents, information assessing the risk with respect to potential contamination with adventitious agents, whether viral or non-viral, as laid down in the relevant guidelines as well as in relevant general monograph and general section of the European Pharmacopoeia, shall be provided.

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

Where applicable and if necessary, a CE marking which is required by the Regulation on Medical Devices, published on the Official Gazette dated 13/03/2002, with no. 24694 shall be provided.

Special attention shall be paid to the following issues.

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), European 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 calculated. For biotechnological medicinal products, the schematic amino acid sequence and relative molecular mass shall be provided, where necessary.

Physicochemical and other relevant properties of the active substance, including biological activity for biological medicinal products shall also be presented.

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

For biological medicinal products, starting materials shall refer to any substance of biological origin such as micro-organisms, organs and tissues of either plant or animal origin, cells (including blood or plasma) of human or animal origin, fluids and biotechnological cell constructs (cell substrates, whether 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 which requires the combination of physicochemical- biological testing, together with the manufacturing process and its control, for the determination of its characteristics and quality and is manufactured or extracted from a biological source.

The following shall be considered as biological medicinal products: immunological medicinal products and human blood; medicinal products derived by recombinant DNA technology, biological controlled expression of the active protein coding-genes, including transformed mammal cells, in prokaryotic and eukaryotic cells and hybridoma and monoclonal antibody methods; advanced therapy medicinal products as defined in Section IV of this Annex.

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 (reactives), culture media, fetal calf serum, additives and buffers involved in chromatography, etc. shall be defined 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. Appropriate information shall be provided for the adequate definition of the manufacturing process and process control.

b) All materials needed in order to manufacture the active substance(s) shall be listed, identifying where each material is used in the manufacturing 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 be documented.

The name, address and responsibility of each manufacturer, including toll manufacturers as well as relevant information pertaining to the proposed manufacturing 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.

With regard to the specific measures to be taken for the prevention of the transmission of animal spongiform encephalopathies, the applicant must demonstrate that the active substance complies with the legislation on minimizing the risk of transmitting animal spongiform encephalopathy agents (BSE/TSE) via medicinal products.

When cell banks are used, the cell characteristics shall be shown to have remained unchanged at the passage level for the use during or after manufacture.

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 its elimination and/or inactivation and this shall be validated.

Where 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 contagious (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. In case of insufficiency of this proof, the attenuation characteristics shall also be demonstrated at the production stage.

The origin of blood products and the criteria and procedures for the collection, transportation and storage of the starting materials shall be described and documented in accordance with provisions laid down in Section III of this Annex.

The manufacturing facilities and equipment shall be described.

d) 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.

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

f) A description and explanation of the significant changes made to the manufacturing process during development and/or manufacturing site of the active substance shall be provided.

3.2.1.3. Characterization of the active substance (s)

Data defining 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 physicochemical and/or immunochemical and/or biological methods, as well as information on impurities shall be provided.

3.2.1.4. Control of active substance (s)

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

The results of control carried out on individual batches manufactured during development stage 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 European Pharmacopoeia shall be used.

3.2.1.6. Container and closure System of the Active Substance

A description of the container and the closure systems and its specifications shall be provided.

3.2.1.7. Stability of the active substance (s)

In line with the guidelines 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.
- 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 content of the finished medicinal product

A description of the finished medicinal product and its content 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 functions of the constituents of:

- the active substance(s),

- the constituent(s) of the excipients, whatever their nature or the quantity used, including coloring matter, preservatives, adjuvants, stabilizers, thickeners, emulsifiers, flavoring and aromatic substances, etc.,
- the constituents of the medicinal product, intended to be taken orally or otherwise administered to the patient (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 primary package (container and closure system), 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 ‘updated terminology’, to be used in describing the structure of medicinal products:

— In respect of the substances which appear in the European Pharmacopoeia, or, failing this, in the national pharmacopoeia, reference shall be made to the relevant pharmacopoeia with the main title at the head of the monograph in question.

— In respect of other substances, the international non-proprietary name (INN) recommended by the World Health Organization (WHO) or, failing this, the exact scientific designation; in the event of substances not having an international non-proprietary name or an exact scientific designation, these 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 coloring matters, those assigned with the code “E” in the “Notification on Coloring Matters Used in Medicinal Products for Human Use”, published on the Official Gazette dated 18/01/2005, with no. 25704 and/or the coloring matters specified in the “Notification, of the Turkish Food Codex, on Coloring Matters Used in Foodstuffs”.

In order to provide the quantitative composition of the active substance(s) of the finished medicinal products, it is necessary, upon consideration of the pharmaceutical form concerned, to specify separately 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 substances 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 authorization for the first time, 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 Organization, 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 section shall be devoted to information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, primary package (container and closure system), microbiological attributes and usage instructions are appropriate for the intended use specified in the marketing authorization 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 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 (Non Clinical 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.
- d) Any overage(s) in the formulation(s) shall be warranted.
- e) As far as the physicochemical and biological properties are concerned, any parameter relevant to the performance of finished product shall be addressed and documented.
- f) 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.
- g) The suitability of the primary package (container and closure) system used for the storage, shipping and use of the finished product shall be documented. A possible interaction between medicinal product and container may need to be considered.
- h) 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 European Pharmacopoeia.
- i) In order to provide appropriate and supportive information for the labeling 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 Article 8 (h), shall be drafted in such a way as to give an adequate synopsis of the nature of the operations employed.

For this purpose, at least the following should be contained:

- specification of the intermediate controls in various stages of manufacture including acceptance criteria, for the assessment of whether the process employed in the manufacture of the pharmaceutical form might have produced any 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,
- the presentation of experimental studies validating the manufacturing process, where a non-standard method of manufacture is used or where it is critical for the product,
- specification of the details pertaining to the sterilization processes and/or aseptic procedures used for sterile medicinal products,
- presentation of a detailed batch formula.

The name, address and responsibility of each manufacturer, including toll manufacturers as well as relevant information pertaining to the proposed manufacturing site or facility involved in manufacturing and testing shall be provided.

b) 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 excipients

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 coloring matters, those assigned with the code “E” in the “Notification on Coloring Matters Used in Medicinal Products for Human Use”, published on the Official Gazette dated

18/01/2005, with no. 25704 and/or the coloring matters specified in the “Notification, of the Turkish Food Codex, on Coloring Matters Used in Foodstuffs”. In addition, coloring matter shall meet purity criteria as laid down in the “Notification, of the Turkish Food Codex, on the Purity Criteria of the Coloring Matters Used in Foodstuffs”.

b) For each excipient, the specifications and their justifications shall be presented in detail. 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 is manufactured in accordance with the legislation on minimizing the risk of transmitting animal spongiform encephalopathy agents via medicinal products (BSE/TSE).

Demonstration of compliance with the aforementioned legislation 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.

d) 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, characterization and controls, with cross references to supporting safety data, both non-clinical 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 section 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 Ministry.

Additional information on toxicity studies with the novel excipient 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 shall comprise 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 sterilization 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 $\pm 5\%$ 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.

3.2.2.7. Primary Package (container and closure) system of the finished medicinal product

A description of the package, container/and the closure system(s) including the identity of each immediate packaging material and their specifications shall be provided.

The specifications shall include description and identification. Where necessary, non-pharmacopoeia methods shall be provided with their validations.

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 medicinal product

In line with the guidelines pertaining to the 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 authorization stability protocol and stability commitment shall be provided.

4. MODULE 4: NON-CLINICAL REPORTS

4.1. Format and Presentation

The general outline of Module 4 shall be as follows:

A - TABLE OF CONTENTS

B -STUDY REPORTS

1- Pharmacology

- Primary Pharmacodynamics
- Secondary Pharmacodynamics
- Safety Pharmacology

- Pharmacodynamic Interactions

2 - Pharmacokinetics

- Analytical Methods and Validation Reports
- Absorption
- Distribution
- Metabolism
- Excretion
- Non-clinical pharmacokinetic interactions
- Other Pharmacokinetic Studies

3- Toxicology

a) Single-Dose Toxicity

b) Repeat-Dose Toxicity

c) Genotoxicity

- In vitro

- In vivo (including supportive toxicokinetic evaluations)

d) Carcinogenicity

- Long-Term studies

- Short- or Medium-Term Studies

- Other studies

e) 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

f) Local Tolerance

4 -Other Toxicity Studies

- Antigenicity

- Immunotoxicity

- Mechanistic studies

- Dependence

- Metabolites

- Impurities

- Other

C- LITERATURE REFERENCES

4.2. Content: Basic Principles and Requirements

Special attention shall be paid to the following issues:

(1) The pharmacological and toxicological tests must contain the following:

a) The potential toxicity of the product 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 product, in both qualitative and quantitative relationship to the proposed use in human beings and all results should be reliable and suit 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) With regard to immunological medicinal products and biological medicinal products such as blood, the requirements of this Module 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 product shall be designed to take account of the possible induction of and interference by, antibodies.

Evaluation pertaining to the reproductive function, embryo/fetal and perinatal toxicity, mutagenic potential and carcinogenic potential shall be considered. Where constituents other than the active substance(s) are incriminated, it may be necessary to validate the results upon the removal of these constituents.

(3) The toxicology and pharmacokinetics 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, 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, recognized 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 obtained 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 pharmacokinetic 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 pharmacodynamic medicinal product interaction, tests on combinations of active substances may be prompted either by pharmacological premises or by indications of therapeutic effect. In the first case, the pharmacodynamic 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 the study of the condition of the active substances and their metabolites within the organism and comprises the study of the absorption, distribution, metabolism (bio-transformation) 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).

Pharmacokinetic investigation of all pharmacologically active substances is necessary. In the case of new combinations of known substances, which have been investigated in accordance with the provisions of this Regulation, pharmacokinetic studies may not be required, if the toxicity tests and therapeutic experimentation justify their omission.

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

A single-dose toxicity test shall refer to a qualitative and quantitative study of the toxic reactions, which may result from a single administration of the active substance or substances contained in the medicinal product, in the proportions and physicochemical state in which they are present in the actual product.

The single-dose toxicity test must be carried out in accordance with the relevant guidelines published by the Ministry.

b) Repeat-dose toxicity

Repeated dose toxicity tests are intended to reveal any physiological and/or anatomic and pathological changes induced by repeated administration of the active substance or combination of active substances under examination and to determine how these changes are related to 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 is defined in the relevant guidelines published by the Ministry.

c) Genotoxicity

The purposes of the study of mutagenic and clastogenic potential is to reveal the changes which a substance may cause in the genetic material 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.

d) Carcinogenicity

Tests to reveal carcinogenic effects shall normally be required:

1. These studies shall be performed for any medicinal product 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 if there is concern about their carcinogenic potential, such as from product 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 is intended to be administered on a chronic basis to humans, a chronic study may be necessary to detect early tumorigenic effects.

e) 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 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 under investigation has been administered to the female during pregnancy.

Conduct of these tests must be adequately justified.

Depending on the indicated use of the medicinal product, additional studies addressing development when administering the medicinal product of the offspring 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 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.

f) Local tolerance

The purpose of local tolerance studies is to ascertain whether medicinal products (both active substances and excipients) 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.

Studies in animals can be substituted by validated in vitro tests. The test results should be of comparable quality and usefulness for the purpose of safety evaluation.

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

5.1.1. 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

- Reports of Hepatic Metabolism and Interaction Studies

- 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 - Reports of Efficacy and Safety Studies

- 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. Content: Basic principles and Requirements

Special attention shall be paid to the following issues.

a) Pursuant to items (l) and (m) of Article 8 and the first item of article 9, the clinical information to be provided shall enable a sufficiently well-founded and scientifically valid opinion to be formed as to whether the medicinal product satisfies the criteria governing the granting of a marketing authorization . Consequently, all of the favourable or unfavourable results of the clinical studies should be notified.

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 must acquaint himself with the conclusions drawn from the pharmacological and toxicological studies and hence the applicant must provide him at least with the investigator's brochure, consisting of all the relevant information known prior to the onset of a clinical trial including chemical, pharmaceutical and biological data, toxicological, pharmacokinetic and pharmacodynamic data in animals and the results of earlier clinical trials, with adequate data to justify the nature, scale and duration of the proposed trial. 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 15 (fifteen) years pursuant to the completion or discontinuation of the trial.

- Relevant documents shall be kept for at least 2 (two) 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, institution 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, institution 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 is no longer authorized.

The marketing authorization holder shall make any additional arrangements for archiving of documentation in accordance with the provisions of the "Regulation Regarding the Drug Investigations", published on the Official Gazette dated 29/01/1993, with no. 21480 and for implementing the guidelines to be drafted on the basis of the referred Regulation.

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

All data and documents shall be made available if requested by the Ministry.

d) The particulars of each clinical trial must contain sufficient detail to allow an objective judgment to be made:

-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 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 trial subject);

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

e) 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 Ministry.

The investigator shall, in his conclusions on the experimental evidence, express an opinion on the safety of the product under normal conditions of use, its tolerance, its efficacy and any useful information relating to indications and contraindications, dosage and average duration of treatment as well as any special precautions to be taken during treatment and the clinical symptoms of over dosage. 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 on behalf of all centers.

f) The clinical observations shall be summarized for each trial indicating:

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) The 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) parameters or evaluation criteria of efficacy and the results in terms of 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.

g) 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;

2) Any interactions that have been observed with other medicinal products 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.
- h) Particulars concerning a new combination of medicinal substances must be identical to those required for new medicinal products and must substantiate the safety and efficacy of the combination.
- i) Total or partial omission of data must be explained. Should unexpected results occur during the course of the trials, further pre-clinical toxicological and pharmacological tests must be undertaken and reviewed.
- j) If the medicinal product 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, reports on in vitro and in vivo correlation studies and bioanalytical and analytical methods shall be provided.

Furthermore, an assessment of bioavailability shall be undertaken where necessary to demonstrate bioequivalence for the medicinal products referred to in item (a) of the first paragraph of Article 9.

5.2.2. Reports of Pharmacokinetic Studies using Human Bio-materials

For the purposes of this Annex, human bio-materials shall refer to any proteins, cells, tissues and related materials derived from human sources that are used in vitro or ex vivo to assess pharmacokinetic properties of drug substances.

In this respect, reports of plasma protein binding study, 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 characteristics shall be described:

- absorption (rate and extent),
- distribution,
- metabolism,
- excretion.

Clinically significant features including the implication of the kinetic data for the dosage regimen especially for patients at risk and differences between man and animal species used in the pre-clinical studies, shall be described.

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, particulars shall be given of joint administration tests performed to demonstrate possible modification of the pharmacological action.

Pharmacokinetic interactions between the active substance and other medicinal products or substances shall be investigated.

5.2.4. Reports of Human Pharmacodynamic Studies

a) The pharmacodynamic action correlated to the efficacy shall be demonstrated including:

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

The pharmacodynamic action 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, particulars shall be given of joint administration tests performed to demonstrate possible modification of the pharmacological action.

Pharmacodynamic interactions between the active substance and other medicinal products or substances shall be investigated.

5.2.5. Reports of Efficacy and Safety Studies

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 of proven therapeutic value, where possible. Any other study design shall be justified. The treatment of the control groups will vary from case to case and will also depend on ethical considerations and therapeutic area. Thus it may, in some instances, be more pertinent to compare the efficacy of a new medicinal product with that of an established medicinal product of proven therapeutic value rather than with the effect of a placebo.

(1) As far as possible and particularly in trials where the effect of the product cannot be objectively measured, preventive measures shall be taken to avoid bias, including methods of randomization and blinding.

(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. 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 guidelines published by the Ministry, 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 implication of the safety evaluation for the possible uses of the medicinal product shall be described.

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 shall be provided.

5.2.6. Reports of post-marketing experience

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

5.2.7. Case Reports Forms and Individual Patient Listings

When submitted in accordance with the relevant Guideline published by the Ministry, 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 present specific features which are such that all the requirements of the marketing authorization application dossier as laid down in Section I of this Annex need to be adapted. Applicants shall present the dossier upon consideration of these particular situations.

1. WELL-ESTABLISHED MEDICINAL USE

For medicinal products the active substance(s) of which has/have a “well-established medicinal use” as referred to in item (a/2) of the first paragraph with recognized efficacy and an acceptable level of safety, the following specific rules shall apply.

The applicant shall submit Modules 1, 2 and 3 as described in Part I of this Annex.

For Modules 4 and 5, a detailed scientific bibliography shall address non-clinical and clinical characteristics.

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

- a) Factors which have to be taken into account in order to establish a well-established medicinal use of constituents of medicinal products 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 a well established medicinal use of a constituent of a medicinal product must not be less than 10 (ten) years from the first systematic and documented use of that substance as a medicinal product.

b) The documentation submitted by the applicant should cover all aspects of the safety and/or efficacy assessment. Relevant literature abstracts should be included or referred to, upon consideration of pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies. All documentation, both favourable and unfavourable, must be presented. With respect to the provisions on “well-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 have been suitably justified, the safety and efficacy of the product may be regarded valid evidences.

c) Particular attention must be paid to any missing information and justification must be provided on the demonstration of an acceptable level of safety and/or efficacy despite the absence of some studies.

d) Non-clinical and/or clinical overviews must explain the relevance of any data submitted for a product other than the product intended for marketing, with the product for which an application has been submitted. A judgement must be made whether the product considered can be regarded as similar to the product for which a marketing authorization application has been submitted, in spite of the existing differences.

e) Post-marketing experience with other products containing the same constituents shall be of particular importance and applicants should put a special emphasis on this issue.

2. ESSENTIALLY SIMILAR MEDICINAL PRODUCTS

a) Applications based upon item (a/1) of the first paragraph of article 9 (essentially similar products) shall contain the data described in Modules 1, 2 and 3 of Part I of this Annex provided that the applicant has been granted the consent of the holder of the original marketing authorization to cross refer to the content of Modules 4 and 5 in his application.

b) Applications based upon item (a/3) of Article 9 (essentially similar products, eg. generics) shall contain the data described in Modules 1, 2 and 3 of Part I of this Annex together with data showing bioavailability and bioequivalence with the original medicinal product provided that the latter is not a biological medicinal product (see Part II, 4 Similar biological medicinal products).

The non-clinical/clinical overviews/summaries of these products shall particularly focus on the following areas:

- 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;
- An evaluation of the bioequivalence studies or a justification why studies have not been performed with respect to the provisions of the “Bioavailability and Bioequivalence Studies” of the “Regulation on Clinical Trials”;
- An update of published literature relevant to the substance and the present application. It may be acceptable for articles in ‘peer review’ journals to be annotated for this purpose;
- Every claim in the summary of product characteristics not known from or inferred from the properties of the medicinal product and/or its therapeutic group, should be discussed in the non clinical/clinical overviews/summaries and substantiated by published literature and/or additional studies.
- Where applicable, additional data in order to demonstrate evidence on the equivalence of safety and efficacy properties of different salts, esters or derivatives of an authorized active substance should be provided by the applicant when he claims essential similarity.

3. ADDITIONAL DATA REQUIRED IN SPECIFIC SITUATIONS

Where the active substance of an essentially similar medicinal product contains the same therapeutic moiety as the original authorised 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 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. SIMILAR BIOLOGICAL MEDICINAL PRODUCTS

The provisions of Article item (a/3) may not be sufficient in the case of biological medicinal products. If the information required in the case of essentially similar products (generics) 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.

When a biological medicinal product as defined in Part I, paragraph 3.2 of this Annex, which refers to an original medicinal product having been granted a marketing authorization in Turkey, is submitted for a marketing authorization by an independent applicant after the expiry of data protection period, the following approach shall be applied.

- Information to be supplied shall not be limited to Modules 1, 2 and 3 (pharmaceutical, chemical and biological data), supplemented with bioequivalence and bioavailability data. The type and amount of additional data (toxicological and other non-clinical 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 need for identified studies foreseen in Modules 4 and 5, shall be required by the Ministry, taking into account the specific characteristic of each individual medicinal product.

The general principles to be applied are addressed in a guideline taking into account the characteristics of the concerned biological medicinal product published by the Ministry. In case the originally registered medicinal product has more than one indication, the efficacy and safety of the medicinal product claimed to be similar has to be justified or, if necessary, demonstrated separately for each of the claimed indications.

5. FIXED COMBINATION MEDICINAL PRODUCTS

Applications based upon item (b) of the first paragraph of article 9 in this Regulation shall relate to new medicinal products made of at least two active substances not previously registered as a fixed combination medicinal product.

For those applications, a full dossier (Modules 1 to 5) shall be provided for the fixed combination medicinal product. Where applicable, information regarding the manufacturing sites and the adventitious agents, safety evaluation shall be provided.

6. DOCUMENTATION FOR APPLICATIONS IN EXCEPTIONAL CIRCUMSTANCES

As provided for in Article 10 of this Regulation, a marketing authorization subject to specific obligations may be granted upon the notification of the applicant, indicating that no comprehensive data may be provided on efficacy and reliability due to following reasons:

- The indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, or
- In the present state of scientific knowledge, comprehensive information cannot be provided, or
- It would be contrary to generally accepted principles of medical ethics to collect such information.

These obligations may include the following:

- The applicant shall complete an identified program of studies within a time period specified by the Ministry, the results of which shall form the basis of a reassessment of the benefit/risk profile,
- The medicinal product in question may be supplied on medical prescription only and may in certain cases be administered only under strict medical supervision, possibly in a hospital and in the case of a radio-pharmaceutical, by an authorized person,
- The package leaflet and any medical information shall draw the attention of the medical practitioners to the fact that the particulars available concerning the medicinal product in question are as yet inadequate in certain specified respects.

7. MIXED MARKETING AUTHORIZATION APPLICATIONS

Mixed marketing authorization applications shall refer to marketing authorization application dossiers where Module 4 and/or 5 consists of a combination of reports of limited non-clinical and/or clinical studies carried out by the applicant and of bibliographical references. Other Modules shall be in accordance with the structure described in Part I of this Annex. The Ministry shall accept the proposed format presented by the applicant on a case-by-case basis.

PART III

PARTICULAR MEDICINAL PRODUCTS

This Part lays down specific requirements related to the nature of identified medicinal products.

1. BIOLOGICAL MEDICINAL PRODUCTS

1.1. Plasma-Derived Medicinal Products

For medicinal products 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:

- Plasma Master File (PMF) shall refer to a documentation, which is separate from the marketing authorization dossier and which provides all relevant detailed information on the characteristics of the entire human plasma used as a starting material and/or a raw material for the manufacture of sub/intermediate fractions, constituents of the excipient and active substance(s), which are part of medicinal products or medical devices referred to in the “Regulation On Medical Devices”, published on the Official Gazette dated 13/03/2002, with no. 24694.
- Every center or establishment for fractionation/processing of human plasma shall prepare and keep updated the set of detailed relevant information referred to in the

Plasma Master File (PMF).

- The Plasma Master File (PMF) shall be submitted to the Ministry by the applicant for a marketing authorization . In case the applicant for a marketing authorization differs from the holder of the Plasma Master File, the Plasma Master File shall be made available to the applicant for submission to the Ministry. In any case, the applicant shall take responsibility for the medicinal product.
- Before taking a decision regarding import product application, the Ministry shall await for the certificate issued by the pharmaceutical authority of the relevant country from which the drug will be imported.
- Any marketing authorization dossier containing a human plasma-derived constituent shall refer to the Plasma Master File (PMF) corresponding to the plasma used as a starting/raw material.

b) Content

In accordance with the provisions regarding the requirements for donors and the testing of donations, the Plasma Master File (PMF) shall include information on the plasma used as starting/raw material, in particular:

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 European 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 in place between the plasma-derived medicinal product manufacturer and/or plasma fractionator/processor on one hand and blood/plasma collection and testing centres or establishments on the other hand, which defines the conditions of their interaction and their agreed specifications.

In addition, the Plasma Master File (PMF) shall provide a list of the medicinal products with ongoing clinical trials and registered products.

c) Evaluation and Certification

- For medicinal products not yet authorized, the marketing authorization applicant shall submit a full dossier to the Ministry, which shall be accompanied by a separate Plasma Master File (PMF) where one does not already exist.

- The Ministry shall conduct a scientific and technical evaluation. If regarded adequate, a certificate of compliance will be issued for the Plasma Master File (PMF).

- The Plasma Master File (PMF) shall be updated and re-certified on an annual basis.

- Changes subsequently introduced to the terms of a Plasma Master File (PMF) shall comply with the provisions of the guidelines implemented on the basis of the amended article 39 of the “Regulation on the Marketing authorization of Medicinal Products for Human Use”, published on the Official Gazette dated 02/03/1995, with no. 22218.

- In line with the abovementioned provisions, the Ministry shall re-evaluate the medicinal products authorized on the basis of the Plasma Master File (PMF), upon consideration of the certification of the associated Plasma Master File (PMF), re-certification and modifications.

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 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:

- Vaccine Antigen Master File shall mean a stand-alone documentation which contains all relevant information regarding biological, pharmaceutical and chemical nature concerning each of the active substances, which are part of the medicinal product.

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 Vaccine Antigen Master File (VAMF) shall contain the following information extracted from the relevant part (active substance) of Module 3 on 'Quality Data' as delineated in Part I of this Annex:

Active Substance

1. General Information, including compliance with the relevant monograph(s) of the European Pharmacopoeia.
2. Information on the manufacture of the active substance: this heading must cover the manufacturing processes, information on the starting and raw materials, specific measures on spongiform encephalopathies agents (TSEs) and adventitious agents safety evaluation and facilities and equipment.
3. Characterisation 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 novel vaccines which contain a novel vaccine antigen, the applicant shall submit to a competent authority a full marketing authorization application dossier including all the Vaccine Antigen Master Files (VAMFs) corresponding to each single vaccine antigen that is part of the novel vaccine. A scientific and technical evaluation of each Vaccine Antigen Master File (VAMF) shall be carried out by the Agency. A positive evaluation shall result in the issuance of a certificate of compliance to the European legislation for each Vaccine Antigen Master File (VAMF) and an evaluation report.

- The provisions of the first paragraph shall also apply to every vaccine, which consists of a novel combination of vaccine antigens, irrespective of whether or not one or more of these vaccine antigens are part of vaccines already registered.

- Changes to the content of a Vaccine Antigen Master File (VAMF) upon its certification shall be subject to the provisions of the relevant guidelines in force, pertaining to variations. Positive evaluations shall be finalized with the issuance of a certificate indicating the compliance of Vaccine Antigen Master File (VAMF).

- As a second step to the provisions in the first, second, third and fourth paragraphs, the Ministry shall take into account the certification, re-certification or variations of the Vaccine Antigen Master File (VAMF) on the concerned medicinal product(s).

2. RADIO-PHARMACEUTICALS AND PRECURSORS

2.1. Radio-pharmaceuticals

For the purposes of this section, applications based upon article 5 and item (u) of article 8, shall provide a full dossier in which the following specific details shall be included:

Module 3

a) In the context of a radio-pharmaceutical kit, which is to be radio-labeled after supply by the manufacturer, the active substance is considered to be that part of the formulation which is intended to carry or bind the radio-nuclide. The description of the manufacturing method of radio-pharmaceutical kits shall include details of the manufacture of the kit and details of its recommended final processing to produce the radioactive medicinal product. The necessary specifications of the radio-nuclide shall be described in accordance, where relevant, with the general monograph or specific monographs of the European Pharmacopoeia. 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 a generator, both mother and daughter radio-nuclides shall be considered as active substances.

b) Details of the nature of the radio-nuclide, the identity of the isotope, likely impurities, the carrier, the use and the specific activity shall be provided.

c) Starting materials shall include irradiation materials.

d) Considerations on chemical/radiochemical purity and its relationship to bio-distribution shall be provided.

e) Radio-nuclide purity, radiochemical purity and specific activity shall be described.

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

g) The requirement to express the content of active substances 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.

h) For kits, the specifications of the finished product shall include tests on performance of products after radio-labelling. Appropriate controls on radiochemical and radio-nuclidic purity of the radio-labelled compound shall be included. Any material essential for radio-labelling shall be identified and assayed.

i) Information on stability shall be given for radio-nuclide generators, radio-nuclide kits and radio-labelled products. The stability during use of radio-pharmaceuticals in vials shall be documented.

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. The evaluation of safety and efficacy of radio-pharmaceuticals shall, therefore, address requirements for medicinal products and radiation dosimetry aspects.

Organ/tissue exposure 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

The results of clinical trials shall be provided where applicable otherwise justified in the clinical overviews.

2.2. Radio-Pharmaceutical Precursors for Radio-Labelling Purposes

In the specific case of a radio-pharmaceutical precursor intended solely for radio-labelling purposes, the primary objective shall be to present information which would address the possible consequences of poor radio-labelling efficiency or in vivo dissociation of the radio-labelled 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 where applicable shall be provided:

Module 3

The provisions of Module 3 shall apply to the marketing authorization of radio-pharmaceutical precursors as defined above in items (a) to (i), where applicable.

Module 4

Concerning single dose and repeat dose toxicity, the results of studies carried out in conformity with the provisions of "Regulation Regarding Good Laboratory Practice Principles and the Documentation of Test Laboratories", published on the Official Gazette dated 25/06/2002, with no. 24796 and in the "Regulation Regarding the Inspection of Good Laboratory Practice and

the Control of the Studies”, published on the Official Gazette with the same date and number 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 on the precursor itself is not considered to be relevant in the specific case of a radio-pharmaceutical precursor intended solely for radio-labelling purposes.

However, information demonstrating the clinical utility of the radio-pharmaceutical 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, including compliance with monograph(s) of the European Pharmacopoeia, shall also apply to the marketing authorization of herbal medicinal products. 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 considered:

1. Herbal substances and herbal preparations:

For the purposes of this Annex, the terms “herbal substances and preparations” shall be considered equivalent to the terms “herbal drugs and herbal drug preparations”, as defined in the European 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 manufacturer of the herbal substance, the name, address and responsibility of each supplier (including toll manufacturers) 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 manufacturer of the herbal preparation, the name, address and responsibility of each manufacturer (including toll manufacturers) 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, including the geographical source of the medicinal plant and cultivation, harvesting, drying and storage conditions.

For the purpose of describing the manufacturing process and process controls for the herbal preparation, information shall be provided to adequately describe the manufacturing process of the herbal preparation, including description of the processing, solvents and markers (reagents), purification stages 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.

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

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.

Justification for the specifications of the herbal substances and herbal preparations 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.

5. ORPHAN MEDICINAL PRODUCTS

In the case of an orphan medicinal product in the meaning of Regulation (EC) No 141/2000, general provisions of Section II-6 (exceptional circumstances) can be applied. The applicant shall then justify in the non-clinical and clinical summaries the reasons for which it is not possible to provide the complete information and shall provide a justification of the benefit/risk balance for the orphan medicinal product concerned.

When an applicant for an marketing authorization for an orphan medicinal product invokes the provisions of Article 10 (1)(a)(ii) and Section II-1 of this Annex (well-established medicinal use), the systematic and documented use of the concerned substance can refer — as way of derogation — to the use of that substance in accordance with the provisions of Article 5 of this Directive.

SECTION IV

ADVANCED THERAPY MEDICINAL PRODUCTS

Advanced therapy medicinal products are based on manufacturing processes focused on various gene transfer-produced bio-molecules and/or biologically advanced therapeutic modified cells as active substances or part of active substances.

For such type of products, the marketing authorization application dossier shall fulfil the format requirements as described in Section I of this Annex.

Modules 1 to 5 shall apply. For the deliberate release in the environment of Genetically Modified Organisms (GMOs), attention shall be paid to the time of establishment in the recipient and to their possible replication and/or modification when released in the

environment. The information concerning the environmental risk should appear in the Annex to Module 1.

1. GENE THERAPY MEDICINAL PRODUCTS (HUMAN AND XENOGENEIC)

For the purposes of this Annex, gene therapy medicinal product shall mean a product obtained through a set of manufacturing processes aimed at the transfer, to be performed either *in vivo* or *ex vivo*, of a prophylactic, diagnostic or therapeutic gene (i.e. a piece of nucleic acid), to human/animal cells and its subsequent expression *in vivo*. The gene transfer involves an expression system contained in a delivery system known as a vector, which can be of viral, as well as non-viral origin. The vector can also be included in a human or animal cells.

1.1. Diversity of Gene Therapy Medicinal Products

a) Gene therapy medicinal products based on allogeneic or xenogeneic cells

The vector is ready-prepared and stored before its transfer into the host cells.

The cells have been obtained previously and may be processed as a cell bank (bank collection or bank established from procurement of primary cells) with a limited viability.

The cells genetically modified by the vector represent an active substance.

Additional steps may be carried out in order to obtain the finished product. By essence, such a medicinal product is intended to be administered to a certain number of patients.

b) Gene therapy medicinal products using autologous human cells

The active substance is a batch of ready-prepared vector stored before its transfer into the autologous cells.

Additional steps may be carried out in order to obtain the finished medicinal product.

Those products are prepared from cells obtained from an individual patient. These cells are then genetically modified using a vector containing the appropriate gene that has been prepared in advance and that constitutes the active substance. The preparation is re-injected into the patient and is by definition intended to a single patient. The whole manufacturing process from the collection of the cells from the patient up to the re-injection to the patient shall be considered as one intervention.

c) Administration of ready-prepared vectors with inserted (prophylactic, diagnostic or therapeutic) genetic material

The active substance is a batch of the prepared vector.

Additional steps may be carried out in order to obtain the finished medicinal product. This type of medicinal product is intended to be administered to several patients.

Transfer of genetic material may be carried out by direct injection of the ready-prepared vector to the recipients.

1.2. Specific requirements regarding Module 3

Gene therapy medicinal products include:

- naked nucleic acid
- complex nucleic acid or non viral vectors
- viral vectors
- genetically modified cells

As for other medicinal products, one can identify the following three main elements of the manufacturing process:

- Starting materials: Materials from which the active substance is manufactured such as, gene of interest, expression plasmids, cell banks and virus stocks or non viral vector;
- Active substance: Recombinant vector, virus, naked or complex plasmids, virus producing cells, in vitro genetically modified cells;
- Finished medicinal product: Active substance formulated in its final immediate container for the intended medical use. Depending on the type of gene therapy medicinal product, the route of administration and conditions of use may necessitate an ex vivo treatment of the cells of the patient (see 1.1.b).

A special attention shall be paid to the following issues:

a) Information shall be provided on the relevant characteristics of the gene therapy of the medicinal product, including its expression in the target cell population. Information concerning the source, construction, characterization and verification of the encoding gene sequence including its integrity and stability shall be provided. Apart from therapeutic gene, the complete sequence of other genes, regulatory elements and the vector backbone shall be provided.

b) Information concerning the characterization of the vector used to transfer and deliver the gene shall be provided. This must include its physicochemical characterization and/or biological/immunological characterization.

For medicinal products that utilize a micro-organism such as bacteria or viruses to facilitate gene transfer (biological gene transfer), data on the pathogenesis of the parental strain and on its tropism for specific tissues and cell types as well as the cell cycle-dependence of the interaction shall be provided.

For medicinal products that utilize non-biological means to facilitate gene transfer, the physicochemical properties of the constituents individually and in combination shall be provided.

c) The principles for cell banking or seed lot establishment and characterization shall apply to gene transfer medicinal products as appropriate.

d) The source of the cells hosting the recombinant vector shall be provided.

The characteristics of the human source such as age, sex, results of microbiological and viral testing, exclusion criteria and country of origin shall be documented.

For cells of animal origin, detailed information related to the following items shall be provided:

- Sourcing of the animals
- Animal husbandry and care
- Transgenic animals (methods of creation, characterization of transgenic cells, nature of the inserted gene)
- Measures to prevent and monitor infections in the source/donor animals
- Testing for infectious agents
- Facilities
- Control of starting and raw materials.

Description of cell collection methodology including location, type of tissue, operating process, transportation, storage and traceability as well as controls carried out during the collection process shall be documented.

e) The evaluation of the viral safety as well as the traceability of the products from the donor to the finished medicinal product, are an essential part of the documentation to be supplied. For instance, the presence of replication competent virus in stocks of non-replication competent viral vectors must be excluded.

2. SOMATIC CELL THERAPY MEDICINAL PRODUCTS (HUMAN AND XENOGENEIC)

For the purposes of this Annex, somatic cell therapy medicinal products shall mean the use in humans of autologous (taken from the patient himself), allogeneic (taken from another human being) or xenogeneic (taken from animals) somatic living cells, the biological characteristics of which have been substantially altered as a result of their manipulation to obtain a therapeutic, diagnostic or preventive effect through metabolic, pharmacological and immunological means. This manipulation includes the expansion or activation of autologous cell populations *ex vivo* (e.g., adoptive immuno-therapy), the use of allogeneic and xenogeneic cells associated with medical devices used *ex vivo* or *in vivo* (e.g., microcapsules, intrinsic matrix scaffolds, biodegradable or not).

Specific requirements for cell therapy medicinal products regarding Module 3

Somatic cell therapy medicinal products include:

- Cells manipulated to modify their immunological, metabolic or other functional properties in qualitative or quantitative aspects;
- Cells sorted, selected and manipulated and subsequently undergoing a manufacturing process in order to obtain the finished medicinal product;
- Cells manipulated and combined with non-cellular components (e.g. biological or inert matrixes or medical devices) and exerting the principle intended action in the finished product;
- Autologous cell derivatives expressed *in vitro* under specific culture conditions;

- Cells genetically modified or otherwise manipulated to express previously unexpressed homologous or non-homologous functional properties.

The whole manufacturing process from the collection of the cells from the patient (autologous situation) up to the re-injection to the patient shall be considered as one single intervention.

As for other medicinal products, the three elements of the manufacturing process are identified:

- Starting materials: Materials from which the active substance is manufactured, i.e., organs, tissues, body fluids or cells;

- Active substance: Manipulated cells, cell lysates, proliferating cells and cells used in conjunction with inert matrixes and medical devices;

- Finished medicinal products: Active substance formulated in its final immediate container for the intended medical use.

a) General information on active substance(s)

The active substances of cell therapy medicinal products consist of cells which as a consequence of in vitro processing display prophylactic, diagnostic or therapeutic properties different from the original physiological and biological one.

This section shall describe the type of cells and culture concerned. Tissues, organs or biological fluids from which cells are derived as well as the autologous, allogeneic, or xenogeneic nature of the donation and its geographical origin shall be documented.

Collection of the cells, sampling and storage prior further processing shall be detailed.

For allogeneic cells, special attention shall be paid to the very first step of the process, which covers selection of donors. The type of manipulation carried out and the physiological function of the cells that are used as active substance shall be provided.

b) Information related to the starting materials of active substance(s)

1. Human somatic cell

Human somatic cell therapy medicinal products are made of a defined number (pool) of viable cells, which are derived from a manufacturing process starting either at the level of organs or tissues retrieved from a human being, or, at the level of a well defined cell bank system where the pool of cells relies on continuous cell lines. For the purposes of this section, active substance shall mean the seed pool of human cells and finished medicinal product shall mean seed pool of human cells formulated for the intended medical use.

Starting materials and each step of the manufacturing process shall be fully documented including viral safety aspects.

I) Organs, tissues, body fluids and cells of human origin

The characteristics of the human source such as age, sex, microbiological status, exclusion criteria and country of origin shall be documented.

Description of sampling including site, type, operating process, pooling, transportation, storage and traceability as well as controls carried out on sampling shall be documented.

II) Cell banking systems

Relevant requirements depicted in section I shall apply for the preparation and quality control of cell banking systems. This may essentially be the case for allogeneic or xenogeneic cells.

III) Ancillary materials or ancillary medical devices

Information shall be provided on the use of any raw materials (e.g., cytokines, growth factors culture media) or of possible ancillary products and medical devices (e.g., cell sorting devices, biocompatible polymers, matrix, fibers, beads) in terms of bio-compatibility, functionality as well as the risk of infectious agents.

2. Animal somatic cells (xenogeneic)

Detailed information related to the following items shall be provided:

- Sourcing of the animals
- Animal husbandry and care
- Genetically modified animals (methods of creation, characterization of transgenic cells, nature of the inserted or excised (knock out) gene)
- Measures to prevent and monitor infections in the source/donor animals
- Testing for infectious agents including vertically transmitted micro-organisms (also endogenous retro viruses)
- Facilities
- Cell banking systems
- Control of starting and raw materials.

a) Information on the manufacturing process of the active substance(s) and the finished product

The different steps of the manufacturing process such as organ/tissue dissociation, selection of the cell population of interest, in vitro cell culture, cell transformation either by physicochemical agents or gene transfer shall be documented.

b) Characterization of active substance(s)

All of the relevant information on the characterisation of the cell population of interest in terms of identity (species of origin, banding cytogenetics, morphological analysis), purity (adventitious microbial agents and cellular contaminants), potency (defined biological activity) and suitability (karyology and tumorigenicity tests) for the intended medicinal use shall be provided.

c) Pharmaceutical development of finished medicinal product

Apart from the specific method of administration used (intravenous infusion, site-injection, transplantation surgery), information shall also be provided on the use of possible ancillary

medical devices (bio-compatible polymers, matrix, fibres, beads) in terms of bio-compatibility and durability.

d) Traceability

A detailed flow chart shall be provided insuring the traceability of the products from the donor to the finished medicinal product.

3. SPECIFIC REQUIREMENTS FOR GENE THERAPY AND SOMATIC CELL THERAPY (HUMAN AND XENOGENIC) MEDICINAL PRODUCTS REGARDING MODULES 4 AND 5

3.1. Module 4

For gene and somatic cell therapy medicinal products, it is recognized that conventional requirements as laid down in Module 4 for non-clinical testing of medicinal products may not always be appropriate due to unique and diverse structural and biological properties of the products in question, including high degree of species specificity, subject specificity, immunological barriers and differences in pleiotropic responses.

The rationale underpinning the non-clinical development and the criteria used to choose relevant species and models shall be properly captioned in Module 2.

It may be necessary to identify or develop new animal models in order to assist in the extrapolation of specific findings on functional endpoints and toxicity to in vivo activity of the products in human beings. The scientific justification for the use of these animal models of disease to support safety and proof of concept for efficacy shall be provided.

3.2. Module 5

The efficacy of advanced therapy medicinal products must be demonstrated as described in Module 5. However, for some products and for some therapeutic indications, however, it may not be possible to perform conventional clinical trials. Any deviation from the existing guidelines shall be justified in Module 2.

The clinical development of advanced therapy medicinal products will have some special features owing to the complex and labile nature of the active substances. It requires additional considerations because of issues related to viability, proliferation, migration and differentiation of cells (somatic cell therapy), because of the special clinical circumstances where the products are used or because of the special mode of action through gene expression (somatic gene therapy).

Special risks associated with such products arising from potential contamination with infectious agents must be addressed in the application for marketing authorization for advanced therapy medicinal products. Special emphasis should be put on both the early stages of development in one hand, (including the choice of donors in the case of cell therapy medicinal products) and on the therapeutic intervention as a whole (including the proper handling and administration of the product) on the other hand.

Furthermore, Module 5 of the application should contain, as relevant, data on the measures to surveying and control of the functions and development of living cells in the recipient, to prevent transmission of infectious agents to the recipient and to minimize any potential risks to public health.

3.2.1. Human Pharmacology and Efficacy Studies

Human pharmacology studies should provide information on the expected mode of action, expected efficacy based on justified end-points, bio-distribution, adequate dose, schedule and methods of administration or modality of use desirable for efficacy studies.

Conventional pharmacokinetic studies may not be relevant for some advanced therapy products. Sometimes studies in healthy volunteers are not feasible and the establishment of dose and kinetics will be difficult to determine in clinical trials. It is necessary, however, to study the distribution and in vivo behaviour of the product including cell proliferation and long-term function as well as the extent, distribution of the gene product and duration of the desired gene expression. Appropriate tests shall be used and, if necessary, developed for the tracing of the cell product or cell expressing the desired gene in the human body and for the monitoring of the function of the cells that were administered or transfected.

The assessment of the efficacy and safety of an advanced therapy medicinal product must include the careful description and evaluation of the therapeutic procedure as a whole, including special ways of administration, (such as transfection of cells ex vivo, in vitro manipulation, or use of interventional techniques) and testing of the possible associated regimens (including immuno-suppressive, antiviral, cytotoxic treatment).

The whole procedure must be tested in clinical trials and described in the product information.

3.2.2. Safety

Safety issues arising from immunological response to the medicinal products or to the expressed proteins, immune rejection, immuno-suppression and breakdown of immuno-isolation devices shall be considered.

Certain advanced gene therapy and somatic cell therapy medicinal products (e.g. xenogeneic cell therapy and certain gene transfer products) may contain replication-competent particles and/or infectious agents.

The patient may have to be monitored for the development of possible infections and/or their pathological sequelae during pre- and/or post-authorization phases; this surveillance may have to be extended to close contacts of the patient including health-care workers.

The risk of contamination with potentially transmissible agents cannot be totally eliminated in the use of certain somatic cell therapy medicinal products and certain gene transfer medicinal products. The risk can be minimized, however, by appropriate measures as described in Module 3.

The measures included in the production process must be complemented with accompanied testing methods, quality control processes and by appropriate surveillance methods that must be described in Module 5.

The use of certain advanced somatic cell therapy medicinal products may have to be limited, temporarily or permanently, to establishments that have documented expertise and facilities for assuring a specific follow up of the safety of the patients. A similar approach may be relevant for certain gene therapy medicinal products that are associated with a potential risk of replication-competent infectious agents.

The long term monitoring aspects for the development of late complications shall also be considered and addressed in the submission, where relevant.

Where appropriate, the applicant has to submit a detailed risk management plan covering clinical and laboratory data of the patient, emerging epidemiological data and, if relevant, data from archives of tissue samples from the donor and the recipient. Such a system is needed to ensure the traceability of the medicinal product and the rapid response to suspicious patterns of adverse events.

4. SPECIFIC STATEMENT ON XENO-TRANSPLANTATION MEDICINAL PRODUCTS

For the purposes of this Annex, xeno-transplantation shall mean any procedure that involves the transplantation, implantation, or infusion into a human recipient of either live tissues or organs retrieved from animals, or, human body fluids, cells, tissues or organs that have undergone ex vivo contact with live non-human animal cells, tissues or organs.

Specific emphasis shall be paid to the starting materials:

- Sourcing of the animals
- Animal husbandry and care
- Genetically modified animals (methods of creation, characterization of transgenic cells, nature of the inserted or excised (knock out) gene)
- Measures to prevent and monitor infections in the source/donor animals
- Testing for infectious agents
- Facilities
- Control of starting and raw materials
- Traceability.