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IMPLEMENTING REGULATION ON MANUFACTURING PLANTS OF MEDICINAL PRODUCTS FOR HUMAN USE

SECTION ONE

Objective, Scope, Legal Basis and Definitions

Objective

ARTICLE 1- (1) The objective of this Implementing Regulation is to regulate principles and procedures pertaining to manufacturing of medicinal products for human use and their active substances including investigational medicinal products in compliance with Good Manufacturing Practices and respective nationally and internationally accepted standards and to implementation of quality assurance system within this framework.

Scope

ARTICLE 2 - (1) This Implementing Regulation covers the manufacturing plants of medicinal products for human use and of their active substances including investigational medicinal product, the imported medicinal products and all operations relating to these products.

(2) Magistral medicinal products are out of the scope.

Legal Basis

ARTICLE 3 - (1) This Implementing Regulation has been prepared based on the Law on Pharmaceuticals and Medicinal Products dated May 14, 1928 No:1262, Article 3(k) of the Health Services Fundamental Law dated May 7,1987 No: 3359 and Article 27 and 40 of Decree Law concerning the Organization and Duties of Ministry of Health and its Affiliated Institutions dated October 11, 2011 No:663.

Definitions

ARTICLE 4 - (1) For the purposes of this Implementing Regulation, the following terms shall bear the following meanings:

a) Independent area: Building area which is isolated by completely being separated from the other areas, departments and rooms of the same manufacturing site through impermeable walls and similar construction material, where the operations are carried out with staff special to the area when necessary and which has separate entrance and exits for staff and materials,

b) Medicinal product for human use: Product containing any natural and/or synthetic active substance or combination of substances which may be used in or administered to human beings with a view to treating or preventing disease, to making a medical diagnosis and to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action,

c) Inspector: Chief Health Inspector, Health Inspector and Assistant Health Inspector working in the Agency,

- ç) Deficiency: Any deficiency observed in the conformity with the principles of Good Manufacturing Practices or in activities required to be carried out in accordance with the marketing authorization file or in documents required according to this Implementing Regulation and its related legislation including documents submitted during the application,
- d) Active substance: Any substance or mixture of substances intended to be used in the manufacture of a medicinal product and that, when used in its production, becomes an active ingredient of that product intended to exert a pharmacological, immunological or metabolic action with a view to restoring, correcting or modifying physiological functions or to make a medical diagnosis,
- e) Manufacturing: Weighing, dividing, processing, primer packaging and secondary packaging processes, making finished products, controlling and batch release activities of starting materials used in the production of medicinal products for human use and/or active substances including investigational medicinal products,
- f) Manufacturer/Manufacturing Plant Authorization Holder: Natural person or legal entity having manufacturing authorization and licence of medicinal products for human use and/or active substances,
- g) History recording: Recording system allowing to monitor the progress of transactions,
- ğ) Importer: Natural person or legal entity having the authorization to import human medicinal products and active substances,
- h) Good manufacturing practices: The part of quality assurance system which ensures that products and active substances are consistently produced and controlled to quality standards appropriate to their intended use as required by the marketing authorization information and product specifications,
- ı) Quality assurance system: The sum total of the organized arrangements made with the object of ensuring that medicinal products for human use are of the quality required for their intended use;
- ı) Quality assurance manager: The person who shall be responsible for implementation of quality assurance system,
- j) Quality control manager: The person who shall be responsible for sampling, making specifications, testing, documenting and approving for the purposes of determining whether medicinal products for human use and active substances and starting materials used in the production of them shall be of required quality throughout manufacturing process from the supply,
- k) Investigational medicinal product: Pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial,
- l) Blinding: Not known of which product was applied to the volunteer during the clinical trial by one or more parties such as the researcher, the investigator, the other researcher, the volunteer or the audience involved in the investigation,
- m) Agency: Turkish Medicines and Medical Devices Agency,

- n) Magistral medicinal product: Medicinal product to be specially prescribed for the patients by the physician and prepared according to this formula in the pharmacy,
- o) Responsible manager: The person having required basic scientific and technical knowledge and experience about medicinal product for human use and active substances including investigational medicinal products as deemed to be responsible person by Agency and concerned firm,
- ö) Immediate packaging: The process of placing the medicinal product for human use to be presented to the end user into the container/package with which it is in contact,
- p) Outer packaging: Procedures of placing inner packaging in contact to medicinal product for human use into outer box/package, replacement of box, printing, barcoding/datamatrix coding, stamping/labelling, adding prospectus /package leaflet, replacement and etc.,
- r) Production manager: The person who shall be responsible for all the production activities,
- s) Manufacturing plant authorization certificate: Authorization certificate given pertaining to manufacturing activities approved by Agency,
- ş) Excipient: Any constituent of a medicinal product other than the active substance and the packaging material.

SECTION TWO

Application, Activities, Responsibilities and Inspection

Application and assessment

ARTICLE 5 - (1) Real persons and legal entities who intend to obtain manufacturing site authorisation shall apply to Agency along with the information and documents specified in Annex 1 of this Implementing Regulation. The manufacturing site authorization holders who will apply for additional activity, shall apply to Agency along with the documents stated in Annex 1 under the title of “Plant”. If lack of any document is determined in the application, the applicant shall be informed by written form. Within no later than 90 days following the acceptance of a complete application and performing inspection by the Agency, the application shall be concluded and it is decided whether manufacturing site authorisation document shall be arranged. The lack of document and delays based on the applicant shall not be included within this 90 days period.

(2) In cases where any change is requested during the phase when the application is assessed, this request shall be examined and concluded within additional 30 days. The period of 30 days shall be suspended until additional details requested by Agency are supplied.

(3) In cases where the manufacturing plant do not comply with the required conditions as a result of the inspection in the manufacturing plant, the Agency shall reject the application. In this case, a new application may be made to the Agency after the identified deficiencies are fulfilled.

(4) Only real persons and legal entities who conduct batch release activity shall apply to the Agency along with the information and documents stated in Annex-2 of this Implementing Regulation.

Certification

ARTICLE 6 - (1) As a result of the inspections or assessment carried out in the manufacturing plants by inspectors that considerations are specified in Article 5 and the requirements of Good Manufacturing Practices are fulfilled, the manufacturing authorisation shall be issued after the acceptance of the application by Agency.

(2) Manufacturing authorisation shall be issued for the manufacturing plant located at the address specified in the application for the activities or pharmaceutical forms including investigational medicinal products in accordance with the determined principles.

(3) Good Manufacturing Practices certificate shall be issued for the authorised manufacturing plants by the Agency based on the applications made.

Executable operations

ARTICLE 7 - (1) Manufacturing of medicinal products for human use and active substances to be put into the market after manufacturing in Turkey within the scope of this Implementing Regulation shall be only carried out in compliance with manufacturing site authorization and the principles and guidelines of Good Manufacturing Practices in manufacturing sites authorised by Agency. This provision shall be applicable to the manufacturing sites which make production only for exportation.

(2) Manufacturing site authorization shall be granted for both total and partial manufacturing activities applied for.

(3) Only medicinal products for human use shall be manufactured in manufacturing sites where medicinal products for human use are produced, however:

a) Without prejudice to legislation provisions arranged by relevant Ministry and Agencies, in manufacturing sites which are granted Manufacturing site Authorisation by Agency, provided that measures are taken by manufacturer to prevent cross contamination risk and approved by the Agency, veterinary medicinal products in applicable form and class and supplementary food with appropriate form shall be produced in same manufacturing sites. The Agency shall request additional measures with qualified staff where necessary.

b) Without prejudice to legislation provisions arranged by relevant Ministry and Agencies, provided that independent area, equipment and independent ventilation systems are used in manufacturing sites of medicinal products for human use having manufacturing site authorization by the Agency; biocidal products administered to human, human tissue and cell products, medical devices and cosmetic products may be produced. In this respect the manufacturer must submit to the Agency a risk assessment document on cross contamination risk within the scope of Good Manufacturing Practices and other guidelines and must get an approval. If this risk assessment report requires further measures, the permission stated in this article shall not be applied. Provided that medical devices are in appropriate form and class and the manufacturer demonstrates that these devices shall not be a risk for the quality of medicinal products for human use and gets the approval of the Agency, a condition for production in independent areas is not required.

Responsibilities of manufacturing authorisation holder

ARTICLE 8 - (1) Manufacturing authorisation holder shall carry out the following responsibilities:

a) Manufacturing authorisation holder shall employ qualified person in line with the Implementing Regulation requirements and production manager, quality assurance manager, quality control manager and sufficient amount of personnel who received appropriate education and/or had sufficient experience in the relevant areas as specified in the Good Manufacturing Practices Guideline.

b) Manufacturing authorization holder shall apply to the Agency assigning a new qualified person having the qualifications stated in this Implementing Regulation within thirty days if qualified person leaves the position in any way.

c) Manufacturing authorisation holder shall provide all the necessary facilities for qualified person to carry out his duties.

ç) Manufacturing authorization holder shall verify that the manufacturers, importers or distributors from whom he obtains active substances are registered with the competent authority of the country in which they are established. Manufacturing authorisation holder shall verify the authenticity and quality of the active substances and the excipients

d) Manufacturing authorisation holder shall enable necessary controls to be made during the intermediate steps of manufacturing process and for the medicinal products for human use and active substances manufactured.

e) Manufacturing authorisation holder shall annihilate unusable or disqualified medicinal products for human use and active substances and excipients in compliance with the related legislation.

f) Manufacturing authorisation holder shall carry out the requirements of the Good Manufacturing Practices Guideline prepared based on this Implementing Regulation.

g) Manufacturing authorisation holder shall enable inspectors to conduct inspection on all the areas, documents and records in the manufacturing plants in any time when deemed necessary.

(2) Manufacturing authorization holder shall enable qualified person, production manager, quality assurance manager and quality control manager to work full-time. Deputies who have the same qualifications shall be appointed by the manufacturing authorization holder to act for them during the periods when they are not on duty temporarily. In case when the qualified person is temporarily absent for over thirty days, the Agency shall be informed about the assignment of deputy. If the duration of the acting exceeds six months, an application should be made to the Agency immediately for the appointment of a new qualified person.

(3) If the manufacturing authorization holder to inform the competent authority and the marketing authorisation holder immediately if he obtains information that medicinal products which come under the scope of his manufacturing authorisation are, or are suspected of being, falsified irrespective of whether those medicinal products were distributed within the legal supply chain or by illegal means, including illegal sale by means of information society services. The products which are subject to falsification in terms of its identity,

origin or distribution history shall be called the falsified products. Therefore, if there are falsifications on;

a) its identity, including its packaging and labelling, its name or its composition as regards any of the ingredients including excipients and the strength of those ingredients;

b) its source, including its manufacturer, its country of manufacturing, its country of origin or its marketing authorisation holder; or

c) its history, including the records and documents relating to the distribution channels used, then such product shall be deemed to be falsified. This definition does not include unintentional quality defects and is without prejudice to infringements of intellectual property rights.

(4) Manufacturing authorisation holder shall verify that the medicinal product is authentic by placing the safety characteristics provided as indicating the medicinal product is authentic and is not tampered with the Regulation on Packaging and Labeling of Medicinal Products for Human Use and published in the Official Gazette dated September 12, 2005 No:25904 without opening the primary packaging of the medicinal product. In addition:

a) Replacement of safety features pertaining to the product shall be made under the conditions of Good Manufacturing Practices in compliance with Pharmaceuticals Track and Trace System.

b) The replacement of the safety features of Pharmaceuticals Track and Trace System is subject to supervision by the Agency.

Qualified person

ARTICLE 9 - (1) Qualified person shall be required to graduate from pharmacy or medicine or to hold bachelor's degree of at least one of the four-year chemistry departments.

(2) If he personally fulfils the conditions laid down in this article, the manufacturing authorisation holder may himself assume the responsibility requirements of the qualified person

(3) The qualified person shall have acquired practical experience over at least two years in one or more undertakings which are authorized to manufacture medicinal products which shall be evidenced by the insurance premium certificates and declaration of the employer in the field of production, quality assurance or quality control activities of medicinal products . However, among people from the occupation groups specified in the first paragraph those who have PhD degree in the relevant fields may act as the qualified person in the manufacturing sites.

(4) Qualified person shall be responsible for conducting batch release by enabling that medicinal products for human use and active substances are manufactured and controlled in compliance with this Implementing Regulation, other legislation in force, the principles of Good Manufacturing and Good Distribution Practices and marketing authorization conditions and for submitting batch records to the inspection of Agency's authorities when requested by keeping them for at least five years.

(5) The document for qualified person agreed to have the requirements specified in this Article shall be issued by the Agency.

Inspections

ARTICLE 10 - (1) Manufacturing plants contained in this Implementing Regulation shall be subject to inspections of Agency. Agency may take samples from medicinal products for human use and active substances. Where necessary, inspections may cover the plants of the marketing authorisation holder. Provided that it is not limited to the provisions of this article, particulars related to inspections are as follows:

a) Manufacturing plants, contracted analysis laboratories for medicinal products for human use and importers shall be subject to routine inspections within the scope of the program created as a result of the risk-based assessment of Agency. These inspections may be performed without notification when necessary.

b) When deemed necessary by the Agency or on the ground of any suspect of non-compliance, Agency shall perform inspections in manufacturing plants or storing, distribution sites of imported active substances and excipients.

(2) Inspectors are authorized to ask for the files and documents considered necessary, from the inspected public or private institutions and from related persons if there is not a legal barrier, analyse them or get their copies approved by competent authorities when deemed necessary; to conduct inspection, examination, counting and investigation in and to take samples from all settled and movable plants subject to inspection and all places where the medicinal products are manufactured, analyzed, stored, distributed, sold or used including manufacturing, storing and distribution sites, to red-tag them when necessary, to stop manufacturing, distribution or sale of them, to sequester, withdraw or recall them, to stop transaction of products via the pharmaceutical track and trace system; and to ask for all kinds of information and help about these matters from all the authorized or related persons and to make the necessary correspondence.

(3) Agency shall enable manufacturing plants, granted manufacturing authorisation by way of inspections specified in first paragraph to operate in compliance with principles and guideline of Good Manufacturing Practices.

(4) After the inspection, time might be granted by the Agency to the inspected manufacturing plant to make assessment and to express an opinion related to the identified issues.

(5) After every inspection as referred to in paragraph 1, the Agency shall report on whether the inspected entity complies with the related legislation in accordance with the report to be prepared.

(6) If the inspections carried out in the manufacturing facilities are subsequently determined to be incompatible with the relevant legislation, the Authority may grant a period of time sufficient to meet the deficiencies to the manufacturing plant in order to complete the identified deficiencies. On-site inspection can be made again if deemed necessary on the expiration of this period to determine whether the deficiencies are remedied or not.

Compliance with Manufacturing Authorisation and Marketing Authorisation of Medicinal Products for Human Use

ARTICLE 11 - (1) Manufacturing authorization/marketing authorisation holder shall be responsible for carrying out manufacturing activities within the scope of information and

documents submitted to, and approved by Agency during the marketing authorisation application. Manufacturer shall be responsible for ensuring compliance of all the manufacturing processes of investigational medicinal products with the information submitted by sponsor to Agency in line with the Regulation on Clinical Trials of Pharmaceuticals and Biological Products published in the Official Gazette dated April 13, 2013 No:28617.

(2) Manufacturer shall periodically review manufacturing methods under the light of scientific and technical advancements including the development of investigational medicinal products.

(3) Manufacturing authorization holder shall be responsible for informing the Agency about the changes to be made related to manufacturing site before these changes are carried into effect, in accordance with the principles determined by the Agency.

(4) Manufacturer shall submit Manufacturing Site Master File to the Agency during the application or shortly after granting of Manufacturing Authorisation. Manufacturing Site Master File is regularly reviewed in line with the changes made in the manufacturing site. In this context, in case of any changes in the Manufacturing Site Master File, updated Master File shall be submitted to Agency.

Medicinal Gases

ARTICLE 12 - (1) Qualified person to be assigned to medicinal gas manufacturing plants shall be required to have practical experience of at least two years in the manufacturing of products fell into the Agency's field of duty.

(2) This provision is not applicable to qualified persons to be assigned to only medicinal gas primary packaging (filling) plants and Article 8(1)(a) shall not be applied for the personnel other than the qualified person.

(3) Principles and procedures relating to medicinal gas importation activities, opening of manufacturing, storing and selling sites and carrying on their activities and to inspections shall be regulated by Agency.

Imported Medicinal Products for Human Use

ARTICLE 13 - (1) Manufacturing plants of imported medicinal products for human use shall be inspected in accordance with the principles and procedures to be determined by the Agency.

(2) After the inspection performed in accordance with the principles and procedures stated in paragraph 1, it is decided whether Good Manufacturing Practices Certificate shall be granted for the imported products.

(3) For the imported human medicinal products, importer shall provide Certificate of Good Manufacturing Practices and / or Manufacturing Authorisation granted by the Agency or by the competent authority of concerned country and accepted by the Agency stating that such products shall meet the requirements of Good Manufacturing Practices regulated by the provisions of this Implementing Regulation. In case of the absence of Certificate of Good Manufacturing Practices granted or accepted by Agency, application shall be made to Agency in compliance with the related guidelines. It is required to be applied to the Agency in line with related guidelines for renewal of the certificate granted by the Agency before the expiration of the validity.

(4) Importer shall ensure that imported medicinal products for human use are provided from the manufacturing plant approved by the competent authority of manufacturing country and, in case of investigational medicinal product importer, this investigational medicinal product has been notified to concerned authority and manufactured by a manufacturer approved by the authority.

(5) Importer shall be responsible for the release of each batch of imported medicinal product for human use to our country's market after conducting necessary tests and controls in accordance with the product marketing authorization file/specifications along with importation. This responsibility shall be fulfilled by a qualified person to be employed by importer.

(6) Agency may require that some or all the tests and analyses mentioned in the previous paragraph to be taken as basis for release into the market of Turkey shall be carried out in Turkey and that batch release shall be approved by qualified person.

(7) Marketing authorization holder shall be responsible for taking the sufficient amount for at least two complete analytic control or Agency-approved amount of samples from each batch of imported medicinal products for human use and keeping the product for at least one year after the expiration date. When requested by the Agency the marketing authorization holder shall submit these samples for analysis to the Agency within one month. The Agency shall reserve the right of requesting to keep these samples in Turkey.

(8) The provisions of Implementing Regulation on Clinical Trials of Pharmaceuticals and Biological Products shall be applied to importation of investigational medicinal products.

Active substances and excipients

ARTICLE 14 - (1) Only active substances which are manufactured in accordance with Good Manufacturing Practices and distributed in accordance with the principles of Good Distribution Practices in compliance with the principles and guidelines of Good Manufacturing Practices shall be used for manufacturing medicinal products for human use.

(2) The holder of the manufacturing authorisation/marketing authorization shall verify compliance of the manufacturer and distributors of active substances with good manufacturing practice and good distribution practices by conducting audits at the manufacturing and distribution sites of the manufacturer and distributors of active substances. The holder of the manufacturing authorisation shall verify such compliance either by himself or, without prejudice to his responsibility as provided for in this Implementing Regulation, through an entity acting on his behalf under a contract. However, this doesn't relieve the manufacturer from liabilities.

(3) Manufacturing authorisation holder shall verify that excipients are suitable for use in human medicinal products by ascertaining the existence of Good Manufacturing Practices or of a quality management system ensuring equivalent standards. In the case of contract manufacturing, this responsibility shall be clearly defined in the contract between the parties. This approval shall be ascertained on the basis of a formalised risk assessment in accordance with the current guidelines. Such risk assessment shall take into account requirements under other appropriate quality systems as well as the source and intended use of the excipients and previous instances of quality defects.

(4) Agency shall take appropriate measures to ensure that the manufacture, import and distribution of active substances, including active substances manufactured in our country that are intended for export, comply with good manufacturing practice and good distribution practices.

(5) Active substances shall only be imported if the following conditions are fulfilled:

a) Active substances shall be manufactured in compliance with the standards of Good Manufacturing Practices Guideline published by the Agency and manufacturing plants of active substances shall be inspected for product groups determined by the Agency.

b) In cases where the inspection shall not be made by the Agency, it is necessary to submit to the Agency in accordance with the related legislation the documents indicating that the active substances to be imported are in compliance with the Good Manufacturing Practice Guidelines of the country concerned or with internationally applicable guidelines.

Special Provisions

ARTICLE 15 - (1) Central radiopharmacy laboratories are subject to the inspection and permission of the Agency. The operations related to these laboratories shall be carried out pursuant to procedures and principles to be determined by the Agency.

(2) The manufacturing plants conducting secondary packaging activities shall store imported products and perform secondary packaging activities related to these products provided that they employ a pharmacist qualified person in accordance with Article 8 of Law on Pharmaceuticals and Medical Preparations. Also the manufacturing plants conducting different production activities in addition to secondary packaging activities shall carry out storing activities of imported medicinal products along with the secondary packaging activities provided that the qualified person of manufacturing plant shall be a pharmacist.

SECTION THREE

Principles of Good Manufacturing Practices

Quality assurance system

ARTICLE 16 - (1) Manufacturer shall establish and implement an effective quality assurance system to provide active participation of the management and personnel of the different departments.

Personnel

ARTICLE 17 - (1) The following considerations shall be applied in the manufacturing plants in terms of personnel;

a) At each manufacturing site, the manufacturer shall have a sufficient number of competent and appropriately qualified personnel at his disposal to achieve the pharmaceutical quality assurance objective.

b) Duties of qualified person and key personnel who shall be responsible for implementing and executing Good Manufacturing Practices shall be defined in job descriptions. Their hierarchical relationships shall be defined in an organisation chart. Organisation charts and job descriptions shall be approved in accordance with the manufacturer's internal procedures.

c) The staff referred to in paragraph 1(b) of this article shall be given sufficient authority to discharge their responsibility correctly.

ç) Personnel shall be included subject to initial training and subsequently periodic trainings on the theory and implementation of Good Manufacturing Practices concepts and quality assurance system as well as specific requirements pertaining to production of investigational medicinal products, if any; and the efficiency of such trainings shall be assessed.

d) Hygiene programs in compliance with the activities in process shall be constituted and monitored through programming appropriate health checks at regular intervals. These programmes shall, in particular, include procedures relating to health, hygiene practice and clothing of personnel.

Premises and equipment

ARTICLE 18 - (1) The following considerations shall be applicable to premises and equipment;

a) Premises and equipment shall be designed, constructed, placed and organized in compliance with the intended operations.

b) Premises and manufacturing equipment shall be laid out, designed and operated in such a way as to minimise the risk of error and to permit effective cleaning and maintenance in order to avoid contamination, cross contamination and, in general, any adverse effect on the quality of the product.

c) Premises and equipment to be used for manufacturing operations, which are critical to the quality of the products, shall be subjected to appropriate qualification and validation.

Documentation

ARTICLE 19 - (1) The following considerations shall be applicable to documentation:

a) The manufacturer shall establish and maintain a documentation system based upon specifications, manufacturing formulae and processing and packaging instructions, procedures and records covering the various manufacturing operations performed.

b) Preestablished procedures for general manufacturing operations and conditions shall be kept available, together with specific documents for the manufacture of each batch. That set of documents shall enable the history of the manufacture of each batch and the changes introduced during the development of an investigational medicinal product to be traced.

c) The batch documentation shall be retained for at least one year after the expiry date of the batches to which it relates or at least five years. Initial and subsequently updated documents submitted to Agency in relation to marketing authorization dossier of the product shall be kept until the marketing authorization is cancelled. For investigational medicinal products, the batch documentation shall be retained for at least five years after the completion or formal discontinuation of the trial in which this manufacturing batch is used.

ç) If the manufacturer uses electronic, photographic or other data processing systems instead of written documents, he/she shall validate the system by which the data will be appropriately stored during the anticipated period of storage. Data stored by this system shall be made readily available in legible form.

d) The electronically stored data shall be protected against loss or damage of data, e.g. by duplication or backup and transfer onto another storage system and data pertaining to process tracks shall be stored and submitted to Agency in writing upon request.

Production

ARTICLE 20 - (1) The different production operations shall be carried out according to pre-established instructions and procedures and in accordance with Good Manufacturing Practice. Adequate and sufficient resources shall be made available for the in-process controls. All the process deviations and product defects shall be documented and thoroughly investigated.

(2) Appropriate technical and organizational measures shall be taken to avoid cross contamination and other mix-ups. In the case of investigational medicinal products, particular attention shall be paid to the handling of products during and after any blinding operation.

(3) Substantial changes in each new manufacturing method or production process pertaining to medicinal products for human use and active substances shall be required to be validated. Critical phases in the manufacturing processes shall be reviewed regularly.

(4) For investigational medicinal products, the manufacturing process shall be validated in its entirety in so far as is appropriate, taking into account the stage of product development. If this is not possible, critical phases shall be validated. All steps in the design and development of the manufacturing process shall be fully documented.

Quality Control

ARTICLE 21- (1) Quality control shall be executed within the framework of the following considerations:

a) The manufacturer shall establish and maintain a quality control system placed under the authority of a person who has the requisite qualifications and is independent of production.

b) That person shall have at his disposal, or shall have access to, one or more quality control laboratories appropriately staffed and equipped to carry out the necessary examination and testing of the starting materials and packaging materials and the testing of intermediate and finished products.

c) During the final control of finished products before their release for sale, distribution or use in clinic investigation, in addition to analytical results, the quality control department shall take into account essential information such as the production conditions, the results of in-process controls, the examination of the manufacturing documents and the conformity of the products to their specifications including the final packaging.

ç) Samples of each batch of finished products shall be retained for at least one year after the expiry date. Samples of starting materials other than solvents, gases and water used in manufacturing process shall be retained for at least two years after the batch release of the product. This period may be shortened if the stability of the starting materials is indicated as shorter in their relevant specifications. Taking samples from starting materials and medicinal products for human use manufactured individually or in small quantities, or when their storage could cause special problems and their storage conditions may be organized separately with the approval of the Agency.

d) For investigational medicinal products, sufficient samples of each batch of bulk products and of the packaging components used for each finished product batch shall be retained for at least five years after completion or formal discontinuation of the clinical trial in which those batches are used.

Contract Manufacturing

ARTICLE 22 - (1) Contract manufacturing shall be executed within the framework of the following considerations:

a) Any manufacturing operation or operation linked thereto which is carried out under contract shall be the subject of a written contract in which mutual responsibilities are expressly stated.

b) The contract shall clearly define the responsibilities between the contract-giver and contract-acceptor including complaints, withdrawals, contracted analysis, and in particular the observance of good manufacturing practice principles by the contract-acceptor and of which party's qualified person shall be responsible for the release of each batch. However, this provision shall not remove the responsibility against the Agency of the parties.

c) The contract-acceptor shall ensure that he/she accepts the principles and guidelines of good manufacturing practice. The contract-acceptor shall meet the obligations related to the inspections carried out by the contract-giver or the Agency.

ç) The contract-acceptor shall not subcontract any of the work entrusted to him under the contract without written authorisation from the contract-giver.

d) If a contracted laboratory is used as a contract-acceptor in Turkey for importers and manufacturers for the analysis based on the batch release of products and for the controls related to manufacturing, it is necessary to obtain permission from the Agency. The principles and procedures about this matter shall be defined by the Agency.

Complaints and Withdrawals

ARTICLE 23 – (1) The manufacturer/marketing authorization holder shall implement a system for recording and reviewing complaints together with an effective system for recalling, promptly and at any time, human medicinal products in the distribution network. Any complaint concerning a defect shall be recorded and investigated by the manufacturer/marketing authorization holder. If the withdrawal of the product is in question as a result of operations conducted, the Agency shall be informed immediately about the matter. If the product is exported to other countries, notification shall be made to these countries pursuant to the Implementing Regulation on Product Withdrawal published in the Official Gazette dated November 19, 2015 No: 29537.

(2) In the case of investigational medicinal products, the manufacturer/marketing authorization holder shall, in cooperation with the sponsor, implement a system for recording and reviewing complaints together with an effective system for recalling promptly and at any time investigational medicinal products in the distribution network. The manufacturer/ marketing authorization holder shall record and investigate any complaint and inform the Agency about any matter which may lead to an unusual limitation in supply or any withdrawal. All research centers and countries in which investigational medicinal products are studied shall be defined. For an investigational medicinal product granted marketing authorization before,

the manufacturer of investigational medicinal product in coordination with sponsor shall inform the marketing authorization holder about any non-compliance which may occur related to the product with marketing authorization. In addition, the sponsor shall establish a system in order to remove blinding from blinded investigational medicinal products promptly provided that he shall reveal the blinded investigational medicinal product only to the extent required by the withdrawal

Self-inspection

ARTICLE 24 - (1) The manufacturer shall conduct self-inspection as part of the quality assurance system in order to take the necessary corrective measures within the scope of good manufacturing practice. Records shall be maintained of such self- inspections and any corrective action subsequently taken.

SECTION FOUR

Miscellaneous and Final Provisions

Database

ARTICLE 25 - (1) A public available database shall be established by Agency and updated information of the authorized manufacturing plants shall be entered to database.

Implementation

ARTICLE 26 - (1) This Implementing Regulation shall be implemented along with the related guideline pursuant to the principles of good distribution and good manufacturing practice.

Sanctions

ARTICLE 27 - (1) For the nature of deficiencies, appropriate time shall be given to the manufacturing plant in order to be completed the deficiencies identified during the inspection performed by the Agency. In cases where there are deficiencies not remedied on the expiration of time entrusted, the manufacturing authorization shall be completely or partially suspended or cancelled. As a result of inspection to be carried out upon the demand of manufacturer for the identification of that the deficiencies or contradictions are remedied, the manufacturing plant shall be allowed to continue its operations, if it is understood that these deficiencies or contradictions are remedied.

(2) In cases where a serious risk which may endanger public health is identified in any of the inspections to be performed in the manufacturing plants, manufacturing activity shall be stopped immediately. Manufacturing authorisation may be suspended or cancelled until such risks are removed.

(3) The manufacturing authorization of manufacturing plant which does not remedy the deficiencies identified during the inspections performed in manufacturing plant and the same deficiencies of which are determined repeatedly, may be completely or partially suspended or cancelled.

(4) The Agency shall make a decision about the products which are on distribution and sale, as they are manufactured before the date of suspending or cancellation, of manufacturing plants of which manufacturing authorization is suspended or cancelled, by taking into consideration the reasons for cancellation or suspending. If the deficiencies which require the manufacturing

authorization to be suspended, are not remedied within a year, the related activities suspended shall be cancelled. If all the activities are suspended, the manufacturing authorization shall be cancelled.

(5) The Agency may completely or partially suspend or cancel the manufacturing authorization of manufacturing plants identified to operate noncompliantly with this Implementing Regulation and good manufacturing practice guidelines.

(6) The authorization of qualified persons of manufacturing plants which are identified to operate noncompliantly with this Implementing Regulation and good manufacturing practice guidelines shall be suspended or cancelled. Then, the manufacturing plant shall assign a new qualified person pursuant to the provisions of this Implementing Regulation and apply to the Agency.

(7) If it is determined three times during the inspections carried out at the manufacturing site that the qualified person is absent without an excuse, his/her qualified person certificate is canceled and a new qualified person is assigned immediately for the manufacturing site and application is made to the Agency.

(8) In case the application is not made to the Agency for a new qualified person in accordance with the provisions of this Regulation within the period specified in Article 8(1)(b), or if it is determined, the manufacturing authorization of manufacturing plant shall be suspended.

(9) The suspension or cancellation of manufacturing authorization shall also be applied for the good manufacturing practice certificate granted by the Agency. However, in cases where the suspension/cancellation are applied for a specific manufacturing activity, the activities included in good manufacturing practice certificate shall be taken into consideration.

(10) In the case of products imported, certificates of Good Manufacturing Practices granted for products manufactured in manufacturing plants which are found to conduct an activity in contradiction of this Implementing Regulation and principles of good manufacturing practice may be suspended or revoked by the Agency.

(11) The marketing authorizations of products in the manufacturing plants which is identified to contradict the provisions of this Implementing Regulation and the principles of good manufacturing practice or of which manufacturing authorization is suspended or cancelled, may be suspended by the Agency.

(12) In the event that the provisions of this Implementing Regulation are violated, the provisions of Law on Pharmaceuticals and Medical Preparations, of Turkish Penal Law dated September 26, 2004 No:5237 and of other related legislations shall be applied.

(13) Manufacturing authorization holders shall be regarded as manufacturer as defined in Consumer Protection Law and shall be responsible for the damage under the conditions specified in this law together with the manufacturing authorization holder.

Cases for which there are no provisions in the Implementing Regulation

ARTICLE 28 - (1) Standards published by national and international institutions and by official authorities shall be applicable to the cases for which there are no provisions in this Implementing Regulation and guidelines of good manufacturing practice published by Agency.

Revoked Regulation

ARTICLE 29 - (1) Implementing Regulation on Manufacturing Plants of Medicinal Products for Human Use published in the Official Gazette dated April 27, 2012 No: 28630 has been revoked.

European Union legislation harmonization

ARTICLE 30 - (1) This Implementing Regulation has been prepared in line with Directive 2001/83/EC on medicinal products for human use, Directive 2003/94/EC laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use and Directive 2011/62/EU on relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products.

Transition Provision

ARTICLE 31- (1) Importers who want to carry out only batch release activities shall be required to get permission from the Agency within one year as of the publication of this Regulation pursuant to this Implementing Regulation.

Entry into force**ARTICLE 32** - (1)

- a) The provisions stated in Article 14(2) of this Implementing Regulation shall enter into force a year after from the publication of this Implementing Regulation,
- b) Other provisions shall enter into force on the date of publication.

Execution

ARTICLE 33 - (1) The provisions of this Implementing Regulation shall be executed by the President of Turkish Medicines and Medical Devices Agency.

ANNEX-I

REQUIRED INFORMATION AND DOCUMENTS FOR THE APPLICATION OF MANUFACTURING PLANT AUTHORIZATION

One who wants to get manufacturing authorization within the framework of Article 5 of this Implementing Regulation shall submit to the Agency the following information and certificates enclosed to their petition ensuring that all the production processes shall be executed in compliance with Good Manufacturing Practices:

1) For company:

- a) Name and address
- b) Original or notarized copy of trade registry gazette

2) For responsible manager:

- a) Curriculum vitae (dated and signed),
- b) Letter indicating that duties and responsibilities are accepted,
- c) Approved copy of diploma or school leave certificate (approved by notary or Health Authority),
- ç) Declaration of employer and / or insurance premium policies indicating that the responsible manager has practical experience for at least 2 years,
- d) Certified copy of id card,
- e) Health report and visual test report updated not earlier than six months,
- f) Written declaration pertaining to criminal record report,
- g) 2 passport photos taken within the last six month,
- ğ) Chamber Registration Certificate from concerned profession chamber (if any),
- h) Discharge Certificate in relation to previous work place.

3) For the key personnel specified in Article 8(1) of this Implementing Regulation:

- a) Curriculum vitae,
- b) Notarized copy of diploma or school leave certificate,
- c) Other documents related to occupational experience

4) For manufacturing plant:

- a) Original or notarized copy of business license,
- b) EIA (Environmental Impact Assessment) decision,
- c) Organizational structure and terms of reference (For key personnel)
- ç) Activities to be carried out and forms to be produced,
- d) Manufacturing flow chart

- e) All products produced in the manufacturing plant apart from the medicinal products for human use and the medicinal products for human use to be manufactured in separated areas,if any.
- f) Building layout plans.
- g) Sketches indicating the material and personnel flows, the pressure differences among areas/chambers, the classification of ventilation for the classified areas, water system flow schema.
- ğ) Activities of contract manufacturing and analysis to be performed by third companies.
- h) Validation master plan (showing the validation/qualification of processes/equipment/system).
- ı) Procedure and instruction list.
- i) Plant master file, if any.

ANNEX-2

REQUIRED INFORMATION AND DOCUMENTS FOR THE APPLICATION OF MANUFACTURING AUTHORIZATION OF PLANTS TO BE CONDUCTED ONLY SERIAL RELEASE ACTIVITIES

Natural persons and legal entities who wants to carry out only serial release activities pursuant to the Article 5(5) of this Implementing Regulation shall submit to the Agency the following information and documents enclosed to their petition:

1) For company:

- a) Name and Address
- b) Original or notarized copy of Trade Registry Gazette.
- c) Original or notarized copy of business license.
- ç) Organizational structure and terms of references (For key personnel).
- d) List of medicinal products for human use to be released, the firms responsible for other manufacturing stages of this products and their addresses (at home and abroad).
- e) Procedure and instruction list.

2) For responsible manager:

- a) Curriculum vitae (dated and signed),
- b) Letter indicating that duties and responsibilities are accepted,
- c) Approved copy of diploma or school leave certificate (approved by notary or Health Authority),
- ç) Declaration of employer and / or insurance premium policies indicating that the responsible manager has practical experience for at least 2 years,

- d) Certified copy of id card,
- e) Health report and visual test report updated not earlier than six months,
- f) Written declaration pertaining to criminal record report,
- g) 2 passport photos taken within the last six month,
- ğ) Chamber Registration Certificate from concerned profession chamber (if any),
- h) Discharge Certificate in relation to previous work place.

3) For the key personnel specified in Article 8(1) of this Implementing Regulation:

- a) Curriculum vitae (dated and signed),
- b) Notarized copy of diploma or school leave certificate,
- c) Other documents related to occupational experience

ANNEX-3

REQUIRED INFORMATION AND DOCUMENTS FOR THE APPLICATION OF MANUFACTURING AUTHORIZATION OF PLANTS TO BE CONDUCTED ONLY OUTER PACKAGING AND STORING ACTIVITIES

One who wants to get manufacturing authorization within the framework of Article 15(2)(1) of this Implementing Regulation shall submit to the Agency the following information and certificates enclosed to their petition ensuring that all the production processes shall be executed in compliance with Good Manufacturing Practices:

1) For Company:

- a) Original or notarized copy of Trade Registry Gazette.

2) For manufacturing plant:

- a) Name, address.
- b) Construction plan approved by the Union of Turkish Engineers and Architects.
- c) Original or notarized copy of business license.
- ç) Sketches indicating the equipment of the plant and the acceptance, quarantine, refusal departments etc.
- d) Personnel list and organizational structure of manufacturing plant.
- e) Document getting from the related authority about that the manufacturing plant is appropriate in terms of fire safety.
- f) Activities to be conducted in the manufacturing plant.

3) For responsible manager:

- a) Curriculum vitae (dated and signed),

- b) Letter indicating that duties and responsibilities are accepted,
- c) Approved copy of diploma or school leave certificate (approved by notary or Health Authority),
- ç) Declaration of employer and / or insurance premium policies indicating that the responsible manager has practical experience for at least 2 years,
- d) Certified copy of id card,
- e) Health report and visual test report updated not earlier than six months,
- f) Written declaration pertaining to criminal record report,
- g) 2 passport photos taken within the last six month,
- ğ) Document approved by Turkish Pharmacists' Association indicating whether he/she is ostracized from profession,
- h) Discharge Certificate in relation to previous work place.

4) For the key personnel specified in Article 8(1) of this Implementing Regulation:

- a) Curriculum vitae,
- b) Notarized copy of diploma or school leave certificate,
- c) Other documents related to occupational experience.