T.C. SAĞLIK BAKANLIĞI
TÜRKİYE İLAÇ VE
TIBBİ CİHAZ KURUMU

REFERENCE GUIDELINES FOR FACILITIES MANUFACTURING MEDICINAL PRODUCTS FOR HUMAN USE

DEPARTMENT OF MEDICINE INSPECTION

This guide is not an interpretation of the current legislation and has been prepared solely to guide applications.

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Contents

1. PURPOSE

This guidelines document has been prepared to provide guidance on the form, content and process of the applications to be made by the facilities willing to obtain an operating permit from Türkiye Medicines and Medical Devices Agency and the facilities that have obtained such operating permit.

2. BASIS

This guidelines document has been prepared based on the Pharmaceutical and Medical Preparations Law with date 14.05.1928 and no. 1262, the Regulation on Manufacturers of Medicinal Products for Human Use, entered into force after being published in the Official Gazette with date 21.10.2017 and no. 30217, and the Communiqué on Manufacturing Sites of Dietary Foods for Special Medical Purposes, entered into force after being published in the Official Gazette with date 13.09.2015 and no. 29474.

In the preparation of this Guide, the document of the European Medicines Agency's "Compilation of Union Procedures on Inspections and Exchange of Information" (EMA/224865/2022 Rev 18 Corr) published on 20/04/2022 in order to facilitate cooperation and compliance in the audit and information exchange procedures carried out by the member states, was used.

3. SCOPE

These guidelines cover the form, content and process of the applications to be made to the Agency by the manufacturers of medicinal products for human use and their active substances and the manufacturing sites of diet foods for special medical purposes, including clinical trial products.

Manufacturing site permits are issued only for the manufacturing site operating in Turkiye, and the scope of the guidelines document is limited to domestic facilities.

In accordance with the relevant legislation, each of the activities of weighing, dividing, processing, primary packaging processes, secondary packaging processes, processing into finished products, relevant inspection and lot release of starting materials used in the manufacture of medicinal products for human use and/or active substances is considered as manufacturing activities. Therefore, in respect to the facilities willing to operate in any of the aforementioned areas, initially an application must be made to our Agency, and consequently an approval must be obtained and a manufacturing site permit must be issued in order to be able to operate. The types of facilities and the scope of their activities for which a

manufacturing site permit shall be issued within the scope of the current legislation are summarized in the table below.

Facility Types Table

Facility type	Code	Scope
Medicinal product manufacturing site	**MS (ÜY)**	Manufacturing activities of all medicinal products for human use and investigational medicinal products or allergen products for human use may be carried out.
Active substance manufacturing facility	**AS (EM)**	Only active substances used in the manufacture of medicinal products for human use and investigational medicinal products for human use may be produced.
Traditional herbal medicinal product facility	**THMP (GBTÜ)**	Only manufacturing activities of traditional herbal medicinal products may be carried out.
Radiopharmaceutical product manufacturing facility	**RF**	Only manufacturing activities of radiopharmaceutical products may be carried out.
Advanced therapy medicinal product manufacturing facility	**ATTP (İTTÜ)**	Only manufacturing activities of advanced therapy medicinal products may be carried out.
Secondary packaging facility	**SPF (SAY)**	Secondary packaging and/or storage activities of medicinal products for human use/investigational medicinal products for human use, and lot release activities only for products for which the manufacturing site permit holder has authorization may be carried out.
Quality Control Laboratory	**AL (AL)**	Only the analysis activities based on lot release of finished products may be carried out.
Lot release facility	**LRF (SSBY)**	Lot release activities only of finished products authorized on behalf of the authorization holder may be carried out. (*If the storage/secondary packaging activities of these products are also to be carried out, permit should be obtained as a secondary packaging facility.*)
Medical gas facility	**MG (MG)**	Only the activities of manufacturing and/or filling medical gases may be carried out.

Dietary food for special medical purposes manufacturing facility	**DFSP (ÖTAG)**	Only the manufacturing activities of dietary foods for special medical purposes may be carried out.

Laboratories that only conduct finished product lot release tests of manufactured and/or imported products must also apply to the Agency within the scope of this guidelines document and obtain relevant permit.

Applications for facilities that will only perform lot release activities must be made in accordance with the **"Lot Release Site Application Guidelines"**,

and applications for facilities that will perform medical gas manufacturing/filling activities must be made in accordance with the **"Medical Gas Manufacturing/Filling Facilities Application Guidelines"**, the details of which are not included in this guidelines document.

4. ABBREVIATIONS AND DEFINITIONS

Unit Domestic Facility Inspections Application and Follow-Up Unit,

Birdek The Risk Assessment Board for Medicinal Products for Human Use, where the applications to be made within the scope of the 3rd paragraph of the 7th article of the Regulation on the Manufacturers of Medicinal Products for Human Use are evaluated,

Document type The titles of the application, service or document type defined under the unit that will evaluate each application in respect to the scope of the application to be made to the Agency,

CAPA Documentation Corrective and preventive action documents showing the actions taken by the company regarding the deficiencies detected in result of the inspection,

DUNS Data Universal Numbering System

EAS Electronic Application System,

EPM Electronic Process Management,

Price tariff The price list, updated at the beginning of each year and published on the website of our Agency, covering the documents issued by the Agenct and the service fees,

Agency Türkiye Medicines and Medical Devices Agency

Facility The place of production where the manufacturing activities are carried out or for which relevant permit is requested,

Product Unless otherwise stated, investigational medicinal products for human use, medicinal products for human use, their active substances or dietary foods for special medical purposes,

Implementing Regulation Implementing Regulation on the Manufacturers of Medicinal Products for Human Use

5. RESPONSIBILITIES OF THE MANUFACTURING SITE OWNER

Natural and legal persons who have obtained a manufacturing site permit within the scope of this guide are responsible of;

- Operating in accordance with applicable legislation, guidelines and standards
- Notifying the Agency of any changes made to the scope of the activities carried out in the facility and obtaining approval if necessary
- Keeping records of activities
- Ensuring GMP standards at the facility
- Providing all kinds of information and documents to be requested by the Agency within the scope of their applications to the Agency

6. APPLICATION PROCESS CHART AND DEFINED DOCUMENT TYPES

The process for the target deadlines shall start on the day the application reaches the Agency in full. In case of a deficiency in the application, the process shall start on the day such deficiency is eliminated.

Subject of Application	Process	Target Deadline	Description/Scope	Document Type	Physical Documentation
Opening	Technical and Administrative	90 days	• Initial permit application • Transfer of facility • Transfer of facility ownership to another company	Medicinal Product / Dietary Food with Special Medical Purpose / Central Radiopharmacy Laboratory / Homeopathy Manufacturing Facility Opening Inspection Traditional Herbal Medicinal Product Manufacturing Facility Opening Inspection Inspection of Contract Analysis Laboratories for Medicinal Products for Human Use Allergen Products Manufacturing Facility Opening Inspection	No
Permit Document	Administrative	30 work days	• Issuance of permit after the opening application • Loss of permit document	Medicinal Product / Dietary Food with Special Medical Purpose / Central Radiopharmacy Laboratory / Homeopathy Manufacturing Facility Permit Document Traditional Herbal Medicinal Product Manufacturing Facility Permit Document Allergen Products Manufacturing Facility Permit Document	No
Additional Activity	Technical and Administrative	90 work days	• Inclusion of an additional activity to approved activities • Changes in production areas • Inclusion of new line within the facility • Major equipment changes	Medicinal Product / Dietary Food with Special Medical Purpose / Central Radiopharmacy Laboratory / Homeopathy Manufacturing Facility Additional Activity Inspection Traditional Herbal Medicinal Product Manufacturing Facility Additional Activity Inspection Additional Activity Inspection of Contract Analysis Laboratories for Medicinal Products for Human Use Allergen Products Manufacturing Facility Additional Activity Inspection	No
Permit Document Update	Administrative	30 work days	• Change of permit holder title • Updating the headquarters address • Transfer of headquarters • Updating the facility address • Adding a new activity after the approval of the additional activity application • Termination of any of the permitted activities	Medicinal Product / Dietary Food with Special Medical Purpose / Central Radiopharmacy Laboratory / Homeopathy Manufacturing Facility Permit Document Update Traditional Herbal Medicinal Product Manufacturing Facility Permit Document Update Allergen Products Manufacturing Facility Permit Document Update	Yes

			• Changes in information indicated under Annex-3		
Responsible Manager Pharmacist Certificate	Administrative	30 work days	• Issuance of certificate for the responsible manager candidate after the approval of the opening application • Appointment of a new responsible manager pharmacist instead of the current responsible manager	Medicinal Product / Dietary Food with Special Medical Purpose / Central Radiopharmacy Laboratory / Homeopathy Manufacturing Facility Responsible Manager Pharmacist Certificate Traditional Herbal Medicinal Product Manufacturing Facility Responsible Manager Pharmacist Certificate Allergen Products Manufacturing Facility Responsible Manager Pharmacist Certificate	Yes
Responsible Manager Pharmacist Certificate Annotation	Administrative	30 work days	• Responsible manager pharmacist name / surname change • Updating the facility address • Change of permit holder title	Medicinal Product / Dietary Food with Special Medical Purpose / Central Radiopharmacy Laboratory / Homeopathy Manufacturing Facility Responsible Manager Pharmacist Certificate Annotation Traditional Herbal Medicinal Product Manufacturing Facility Responsible Manager Pharmacist Certificate Annotation Allergen Products Manufacturing Facility Responsible Manager Pharmacist Certificate Annotation	Yes
Responsible Manager Pharmacist Authorization and Proxy Information	Administrative	-	• Proxy notification for the period of leave of the responsible manager	Responsible Manager Pharmacist Authorization/Proxy Statement	No
Good Manufacturing Practices Certificate	Administrative	30 work days	• Issuance of GMP certificate and/or Responsible Manager Certificate to the facility after the manufacturing site permit issuance	GMP Certificate (Turkish and English - for Domestic Manufacturing Facilities) Manufacturing Licence	No
Corrective and Preventive Action Documentation	Technical and Administrative	30 work days	• Submission of CAPA document after the inspections carried out at the facility	Corrective and Preventive Action Documentation	No
Facility Master File	Administrative	-	• Submission of facility master file to Agency	Update of Facility Master File	No
Inspection Book	Administrative	30 work days	• After the issuance of the manufacturing site permit following opening • In case of need for new inspection book	Domestic Facility Inspection Book	No
Key Personnel Change	Administrative	-	• Key personnel changes other than responsible manager pharmacist	Manufacturing Site Key Personnel Change (except Responsible Manager)	No
Foreign Authority Inspection	Technical and Administrative	-	• Inspection of the facility by relevant authority of another country	Facility Inspection by Abroad Authorities	No
Facility Closure	Administrative	30 work days	• Termination of all activities by the permit holder at the facility	Facility Closure Processes	Yes

- For applications related to transactions or processes that are not included in the table above but are considered to be within the scope of duty of our unit, the document type "**Other Transactions of Manufacturer**" should be used.
- For submitting additional documents for an application already made, the document type "**Application Completion**" should be used.
- For mandatory cases where it is necessary to submit physical documents for an application for which physical documents are not accepted, the document type "**Physical Document Delivery (For Domestic Facilities)**" should be used.

7. GENERAL WARNINGS

- For all application types, the company must be registered in the Electronic Application System by the applicant before applying.
- In the case of applications of companies under the same partnership, if the permit will be issued on behalf of the affiliated company, branch, etc., the EAS system must be registered in the name of the affiliated company / branch company and the application must be made through this registry.
- Applications made in the wrong document type shall be returned without being evaluated.
- In all applications made within the scope of this guide, document types are defined under the "Domestic Facility Inspections Application and Follow-up Unit" under the "Department of Medicine Inspection".
- In accordance with the EPM Company User's Guide, applications that require the delivery of physical documents must be submitted to the Agency within 30 days, otherwise the applications shall be cancelled. The e-follow-ups of the applications that require physical documents but are not entered into the Agency documentation and/or the attachments are marked to be uploaded from the kiosk but are not loaded within 30 days shall be canceled on the 31st day. Thus, in document types that require physical documents, physical documents must be entered to the Agency registry in order for the documents to be processed.
- Regarding document types for which the physical documentation tab is specified as **"no"**, **physical documents shall not be accepted** .
- Regarding document types for which the physical documentation tab is specified as **"yes"**, the application shall not be forwarded to the unit unless the relevant physical document reaches the Agency.
- The service or document fees regarding application may be accessed from the price tariff list published on the website of our Agency.
- Physical documents shall be not accepted for the applications to the Domestic Facility Inspections and Application Follow-Up Unit, unless otherwise stated. It shall be sufficient to electronically submit a notarized copy of the documents for which a notarized copy is requested in accordance with the legislation.

It is strongly requested to avoid unnecessary stationery and paper use in all applications to be made within the scope of this guidelines document.

8. APPLICATION METHOD, CONTENT AND PROCESS

8.1 Opening

- Natural or legal persons willing to carry out manufacturing activities related to the products covered by this guidelines document should apply to the Agency, subjected to inspection by the Agency in terms of good manufacturing practices and, if found appropriate, and then commence their activities.
- The opening application covers the applications of companies willing to start operating for the first time, as well as the cases where the existing authorized facilities are **moved** to another address or the facility is **transferred** to a different legal entity.
- In the event that a facility that has received permission only for the traditional herbal medicinal product manufacturing activity or only for the finished product analysis activity based on lot release, later on extends the scope of the permit and wants to manufacture medicinal products for human use, a reapplication should be made to the Agency with the "Medical Product / Dietary Food for Special Medical Purposes / Central Radiopharmacy Laboratory / Homeopathy Production Facility Opening Inspection" document type and the **facility should undergo the opening inspection anew**.
- A facility that could not get approval due to the deficiencies detected in the facility in result of the opening inspection must eliminate the deficiencies identified in the inspection within **one year** (unless additional time is deemed appropriate by the inspector performing the inspection) following the notification of the deficiencies. The applicant who fails to eliminate the deficiencies within one year must apply for the opening inspection again in order to receive approval.
- The inspection to be carried out at the facility by the Agency inspectors shall be limited to the scope of the application. Therefore, the application dossier must be prepared in such a way as to include all the activity permits to be requested.

The facility must have completed the following preparations prior to the inspection:

- Completion of the construction of the facility building
- Obtaining the workplace license issued by the competent authority
- A quality system must be documented and implemented in accordance with the requirements of the activities to be carried out at the facility. The current quality system should include procedures, records and instructions for the following activities to be carried out.
    - quality systems such as deviation, change control, risk management, product quality
    - documentation
    - materials
    - manufacturing activities
    - personnel matters, including hygiene and training
    - validation and qualification

  - equipment assembly and calibration
  - maintenance, cleaning and sanitization
  - environmental control
  - pest control
  - complaints
  - recalls
  - internal inspection
  - laboratory controls and processes
  - lot release actions and processes
- identification of facilities, buildings and equipment in accordance with the activities to be carried out at the facility
- documentation and approval of validation and qualification protocols for all activities and equipment in the facility, including cleaning
- personnel responsible for production, quality control and quality assurance having been recruited, assigned and adequately trained

Facilities that will carry out manufacturing activities are required to submit the documents under **Annex-1 of the Regulation**, and facilities that will only engage in secondary packaging activities are required to submit the documents under **Annex-3 of the Regulation**.

Secondary packaging activities are limited to the following headings under the Manufacturing Site Permit. Facilities willing to operate outside of such activities must apply within the scope of **Annex-1 of the Regulation**.

1.5 Packaging
1.5.2 Secondary Packaging

2.3 Other Import Operations
2.3.1 Facility for Physical Importation

1.4 Other Investigational Medicinal Products for Human Use or Manufacturing Activities
1.4.3 *Others (Clarify)*
- Storage of active substances/raw materials

*Companies that will carry out the lot release operations and secondary packaging/storage operations **of their own authorized products** may also choose the lot release activities listed below. In accordance with the legislation, the lot release activity may only be carried out by **the company holding the marketing authorization**. Therefore, the titles below are valid only for the lot release activities of the products for which they have their own marketing authorization, and may not be applied for the lot release activities of the authorized products of other companies.

Section 1- Manufacturing Operations
1.1 Sterile Products
1.1.3 Lot Release Operations

1.2 Non-sterile Products
1.2.2 Lot Release Operations
1.3 Biological Medicinal Products
1.3.2 Lot Release Operations
1.3.2.1 Blood Products
1.3.2.2 Immunological Products
1.3.2.3 Cell Therapy Products
1.3.2.4 Gene Therapy Products
1.3.2.5 Biotechnological Products
1.3.2.6 Human or Animal Extract Derived Products
1.3.2.7 Tissue Engineering Products
1.3.2.8 Other Biological Medicinal Products (Clarify)

2.2 Lot Release Of Imported Medicinal Products
2.2.1 Sterile Products
2.2.1.1 Aseptically Prepared Products
2.2.1.2 Terminally Sterilized Products
2.2.2 Non-sterile Products
2.2.3 Biological Medicinal Products
2.2.3.1 Blood Products
2.2.3.2 Immunological Products
2.2.3.3 Cell Therapy Products
2.2.3.4 Gene Therapy Products
2.2.3.5 Biotechnological Products
2.2.3.6 Human or Animal Extract Derived Products
2.2.3.7 Tissue Engineering Products
2.2.3.8 Other biological medicinal products *(Clarify.)*

8.1.1. Opening Application

- Within the scope of the legislation, apply to the Agency with a cover letter, Opening Application Form and supporting documents, in the appropriate document type.
    - **a.** For facilities of which field of activity comprises solely of traditional herbal medicinal products, an application in the document type *"Traditional Herbal Medicinal Product Manufacturing Site Opening Inspection"* shall be required.
    - **b.** For facilities of which field of activity comprises solely of analysis activities based on lot release of finished products, an application in the document type *"Medicinal Products for Human Use Contract Analysis Laboratories Inspection"* shall be required.
    - **c.** For facilities of which field of activity comprises solely of allergen products, an application in the document type *"Allergen Products Manufacturing Facility Opening Inspection" shall be required.*
    - **d.** *For all other facilities, an application shall be made in the document type* "Medicinal Product/Dietary Food for Special Medical Purposes/Central Radiopharmacy Laboratory/Homeopathy Manufacturing Facility Opening Inspection".
- Within the scope of relevant application, the appropriate application form shall be filled in completely in digital environment.
- Together with the application form, the documents included in the annex of the Regulation and specified in detail at the end of the application form shall be uploaded to the system in full.
- After the application reaches the Agency, the documents pertaining to the application shall be evaluated by the Agency and any deficiencies, if any, shall be notified in writing.

- In case of deficiencies, complete the relevant deficiencies and repeat the application. This process shall be repeated until a complete application is made.
- When no deficiency is detected in the application by the Agency or all the deficiencies reported are corrected by the applicant, the application shall be approved and an accrual shall be created for relevant payment.
- Following the payment of the inspection fee, the inspection planning process shall be initiated by the Agency.
- The result of the inspection report prepared in conclusion of the inspection carried out at the facility by the Agency inspectors shall be notified in writing to the applicant.
- Documents indicating that the shortcomings reported in result of the report have been completed shall be sent to the Agency as specified in the Corrective and Preventive Action Document title.
- In the event the facility application is approved at the end of the inspection process, the applicant shall be notified in writing that a permit and a responsible manager certificate may be issued.
- Following the approval letter, apply for the permit and the responsible manager certificate as specified under the titles of the Permit Document and Responsible Manager Certificate.

8.1.2. Filling the Opening Application Form

- *Active Substance Manufacturing Site Opening Application Form and Active Substance Manufacturing Form shall be filled for* active substance facilities*, and Opening Application Form shall be filled for* all other facilities*.*
- If both medicinal product for human use and investigational medicinal product for human use will be produced at the facility, two separate opening application forms must be filled.
- Only one facility type may be selected when selecting facility type.
  - Responsible manager pharmacist candidate must be graduated from pharmacy, medicine or one of the branches of chemistry providing at least four years of undergraduate education in accordance with Article 9 of the Regulation. However, the provision referred to in Article 5 of the Law No. 1262 is applied to the responsible manager candidates of the Quality Control Laboratories that make application to carry out analysis activities based on batch release of finished products.
- Persons who have a doctorate degree in the relevant field among the professionals stipulated in the 3rd paragraph of the Article 9 of the Regulation may be appointed as the responsible manager without seeking 2 years of practical experience.
  - Pursuant to Article 8 of the Regulation, it is obligatory to employ a production manager, quality assurance officer and quality control officer with sufficient experience in manufacturing facilities. However, in applications to be made for the Quality Control Laboratory facility type, it is sufficient to employ a responsible manager as key personnel.
- It is essential that the responsible manager, production manager, quality assurance officer and quality control officer are employed on full time basis.

- In addition to the responsible manager candidate, the curriculum vitae, diploma and professional inspection documents also of the production manager, quality assurance officer and quality control officer should be submitted in the annex to the application.

8.1.3 Activities to be Carried Out

Details of manufacturing activities of active substances are given under 8.1.3.1,
and details of manufacturing activities of medicinal products for human use and investigational medicinal products for human use are given under 8.1.3.2.

8.1.3.1 Active Substance Manufacturing Facility Activities

MANUFACTURING PROCESSES

Active Substance:

In the active substance manufacturing form, the name of the substance/active substance that is planned to be manufactured shall be entered in the *Active Substance Name* field and the manufacturing processes to be carried out for this active substance shall be selected from the appropriate headings classified from A to E. If more than one active substance is to be manufactured , the appropriate process steps between headings A and E should be filled out separately for each active substance. The production steps to be carried out should be clearly defined in the *Active Substance Manufacturing Form* filled in this manner for each active substance. If only the "intermediate product" of an active substance is manufactured and the finished active substance is not manufactured, then the name of the " Medicinal Active Substance Intermediate Product" should be entered in the "Active Substance" field and the related manufacturing processes should be defined as described above.

A Manufacture of Medicinal Active Substances through Chemical Synthesis

Item 1 in this section may include any step from the production of the defined starting material to the production of the raw active substance.

A.1. Manufacture of Medicinal Active Substance Intermediary Product
A.2. Manufacture of Raw Medicinal Active Substances
A.3. Salt Formulation/Purification Steps (Crystallization etc.) *(Explain.)*
A.4. Other *(Clarify.)*

B Manufacture of Medicinal Active Substances through Extraction from Natural Sources

Item 5 in this section refers to the chemical modification of the extracted active ingredient. Activities such as drying or grinding are included under *General Final Production Stages (E)*.

B.1. Extraction of Substance from Herbal Source
B.2. Extraction of Substance from Animal Source
B.3. Extraction of Substance from Human Source
B.4. Extraction of Substance from Mineral Source
B.5. Modification of Extracted Substance *(Source should be cited: 1,2,3,4)*
B.6. Purification of Extracted Substance *(Source should be cited: 1,2,3,4)*
B.7. Other *(Clarify.)*

C **Manufacture of Medicinal Active Substances through Biological Processes**

C.1. Fermentation
C.2. Cell Culture *(Cell type must be specified. Mammal, bacteria, etc.)*
C.3. Isolation/Purification
C.4. Modification
C.5. Other *(Clarify.)*

D **Manufacture of Sterile Medicinal Active Substances** (where applicable, fields coded as A, B and C should also be filled.)

This field shall be filled in to record the production steps that render the medicinal active substance sterile.

D.1. Aseptic Preparation
D.2. Terminal Sterilization

E **General Final Production Stages**

E.1. Physical Process Stages *(Must be defined. Drying, grinding/micronization, screening etc.)*
E.2. Primary Packaging *(closing / sealing the active substance with the packaging material with which it is in direct contact)*
E.3. Secondary Packaging *(placement of the sealed primary packaging in the outer packaging material or container. This process also includes labeling for identification or traceability purposes.)*
E.4. Other *(Clarify.)*

F **Quality Control Tests** (This field may be filled if any section from fields A,B,C,D,E is filled.)

If the only activity to be performed for active substances in the relevant facility is quality control tests, an application should be made for these facilities within the scope of the "Quality Control Laboratory" facility type.

F1. Chemical/physical testing
F2. Microbiological (non-sterile) testing
F3. Microbiological (sterile) testing
F4. Biological testing

8.1.3.2 Activities of Facilities Manufacturing Medicinal Products for Human Use / Investigational Medicinal Products for Human Use

SECTION 1 MANUFACTURING PROCESSES

1.1 Sterile Products

After selecting the main titles numbered below in the Opening Application Form, the dosage forms to be produced for each main title are to be indicated in the box under the heading based on the *Pharmaceutical Dosage Form List* in the annex of this guideline. Since the list is prepared according to the electronic database in the EPM, **the dosage forms in the list should be specified under the correct heading**.

As the primary packaging of sterile products is considered as a part of manufacturing, it is included under this heading. Therefore, if the dosage form produced is limited to a certain primary packaging, this limitation should be stated separately in the explanation/restriction field under the relevant heading.

Care should be taken to select title for each activity carried out in the facility without missing any.

1.1.1 Aseptically Prepared Products
1.1.1.1 Large Volume Liquids
1.1.1.2 Lyophilisates
1.1.1.3 Semi Solids
1.1.1.4 Small Volume Liquids
1.1.1.5 Solids and Implants
1.1.1.6 Other Aseptically Prepared Products(Clarify)

1.1.2 Terminally Sterilized Products
1.1.2.1 Large Volume Liquids
1.1.2.2 Semi Solids
1.1.2.3 Small Volume Liquids
1.1.2.4 Solids and Implants
1.1.2.5 Other Terminally Sterilized Products (Clarify.)

1.1.3 Lot Release Operations

1.2 Non-sterile products

After selecting the main titles numbered below in the Opening Application Form, the dosage forms to be produced for each main heading are to be indicated in the box under the heading based on the Pharmaceutical Dosage Form List in the annex of this guideline. Dosage forms in the list should be stated under the correct heading.

1.2.1 Non-sterile Products
1.2.1.1 Capsules, Hard Shell
1.2.1.2 Capsules, Soft Shell
1.2.1.3 Medicated Chewing-Gum
1.2.1.4 Impregnated Matrices
1.2.1.5 Liquids for External Use
1.2.1.6 Liquids For Internal Use
1.2.1.7 Medicinal Gases
1.2.1.8 Other Solid Dosage Forms

1.2.1.9 Pressurised Products
1.2.1.10 Radionuclide Generators
1.2.1.11 Semi Solids
1.2.1.12 Suppositories
1.2.1.13 Tablets
1.2.1.14 Transdermal Patches
1.2.1.15 Other Non-Sterile Products (Clarify.)

1.2.2 Lot Release Operations

1.3 Biological Medicinal Products

Where a facility performs any production steps associated with the manufacture of biological products, the following product categories should be used for identifying the product. In the case of the manufacture of biological material as part of the processing steps in the manufacture of the finished biological product, these processes should be specified in the appropriate heading under this section.
In case the permitted activities also include the manufacture of the finished dosage form of the biological product, the relevant dosage form must be selected separately in the manufacturing site permit.

1.3.1 Biological Medicinal Products
1.3.1.1 Blood Products
1.3.1.2 Immunological Products
1.3.1.3 Cell Therapy Products
1.3.1.4 Gene Therapy Products
1.3.1.5 Biotechnologic Products
1.3.1.6 Human or Animal Extract Derived Products
1.3.1.7 Tissue Engineering Products
1.3.1.8 Other biological medicinal products (Clarify.)
1.3.2 Lot Release Operations
1.3.2.1 Blood Products
1.3.2.2 Immunological Products
1.3.2.3 Cell Therapy Products
1.3.2.4 Gene Therapy Products
1.3.2.5 Biotechnological Products
1.3.2.6 Human or Animal Extract Derived Products
1.3.2.7 Tissue Engineering Products
1.3.2.8 Other Biological Medicinal Products (Clarify)

1.4 Other Products or Manufacturing Activities

In cases where the facility carries out the processing steps related to herbal or homeopathic dosage forms (e.g. tablets), the headings of the relevant dosage form (section 1.1 to section 1.2) should be filled out in addition to the following headings. In the event the facility only carries out processes related to the manufacture of herbal or homeopathic products, an explanatory note regarding dosage forms/manufacturing processes ('herbal product only' or 'homeopathic product only') must be written on the manufacturing site permit.
1.4.2 Medicinal Active Substance/Excipient/Finished Product Sterilization item shall be selected when sterilization processes are not carried out as part of the manufacture of a dosage form. For instance, if it is a facility that provides contracted gamma ray sterilization services to other

manufacturers of medicinal products for human use, necessary arrangements shall be made under this section.
Example for item 1.4.3 Other (Explain):
'Storage' - (for instance, if lot release of medicinal products for human use is carried out by storing only in the facility, the storage process shall be indicated under this heading.)

1.4.1 Other products
1.4.1.1 Herbal Products
1.4.1.2 Homeopathic Products
1.4.1.3 Other (Clarify)
1.4.2 Sterilization of Active Substances/Excipients/Finished Products
1.4.2.1 Filtration
1.4.2.2 Dry Air
1.4.2.3 Steam
1.4.2.4 Chemical
1.4.2.5 Gamma Radiation
1.4.2.6 Electron Beam
1.4.3 Others (Clarify)

1.5 Packaging Activities

Headings pertaining to the primary packaging of non-sterile products are covered under this heading. The primary packaging of a sterile product is covered by the processing steps under Section 1.1, unless otherwise explained/limited to the relevant dosage form.

Example for item 1.5.1.15 “Other Non-Sterile Products”

If the permit holder will carry out the primary packaging of a dosage form (e.g. implants) that has not been manufactured in the facility and will then be terminally sterilized in final container, this activity shall be regulated under the heading 1.5.1.17.
“ 1.5.1.15: Primary packaging of implants to be terminally sterilized”

1.5.1 Primary Packaging
1.5.1.1 Capsules, Hard Shell
1.5.1.2 Capsules, Soft Shell
1.5.1.3 Medicated Chewing-gum
1.5.1.4 Impregnated Matrices
1.5.1.5 Liquids for External Use
1.5.1.6 Liquids For Internal Use
1.5.1.7 Medical Gasses
1.5.1.8 Other Solid Dosage Forms
1.5.1.9 Pressurized Products
1.5.1.10 Radionuclide Generators
1.5.1.11 Semi Solids
1.5.1.12 Suppositories
1.5.1.13 Tablets
1.5.1.14 Transdermal Patches
1.5.1.15 Other Non-Sterile Products (Clarify)
1.5.2 Secondary Packaging

1.6 Quality Control Testing

In case quality control tests based on lot release of the products manufactured will also be carried out at the facility, these tests should be specified under this section.

Only this field should be filled in applications for the Quality Control Laboratory (AL) facility type**that applies only to carry out analysis activity based on batch release of finished products.**

This heading covers only the quality control tests of domestic medicinal products for human use; for the quality control tests of imported medicinal products for human use, the title 2.1 Quality Control Tests of Imported Medicinal Products should be selected.

1.6.1 Microbiological (sterility)
1.6.2 Microbiological (non-sterility)
1.6.3 Chemical/Physical
1.6.4 Biological

SECTION 2 Import Procedures For Medicinal Products For Human Use

2.1 Quality Control Testing Of Imported Medicinal Products

In the case of quality control tests of imported human medicinal products conducted at the facility, the categories of permitted tests shall be specified according to the options below. Even if the facility permit document has been arranged according to the 1.6 Quality Control Tests Title, if quality control tests are also carried out for imported products, this section shall also be filled out.

2.1.1 Microbiological (Sterility)
2.1.2 Microbiological (Non-Sterility)
2.1.3 Chemical/Physical
2.1.4 Biological

2.2 Lot Release Of Imported Medicinal Products

This title should be filled out in the case where the release processes of the imported finished product or the bulk dosage form that will be processed for primary packaging are carried out at the facility. In the event the permit holder will also realize the physical import of the imported product (such as the storage of the products), the necessary explanation should be made under the heading 2.3.1.

In accordance with the legislation, the permit holder may only carry out the lot release of imported products for which they hold marketing authorization.
In the event that the release of imported comparator products for Investigational Medicinal Products for Human Use (Annex-2) will be carried out, an explanation regarding the relevant heading shall be specified from the categories below.

2.2.1 Sterile Products
2.2.1.1 Aseptically Prepared Products
2.2.1.2 Terminally Sterilized Products
2.2.2 Non-sterile Products
2.2.3 Biological Medicinal Products
2.2.3.1 Blood Products
2.2.3.2 Immunological Products

2.2.3.3 Cell Therapy Products
2.2.3.4 Gene Therapy Products
2.2.3.5 Biotechnological Products
2.2.3.6 Human or Animal Extract Derived Products
2.2.3.7 Tissue Engineering Products
2.2.3.8 Other biological medicinal products (Clarify.)

2.3 Other Import Operations

Filling out this heading means that the facility may receive and store imported products for lot release process. The product groups within the scope of the lot release process should be specified separately under the relevant headings in the heading 2.2.

The imported intermediate product type should be specified in detail.

e.g.: granule, sterile active substance, partially manufactured biological product

2.3.1 Facility for Physical Importation

Choosing this activity means that imported products that will be held for lot release may be stored at the facility. However, in accordance with Article 15 of the Regulation and Article 8 of the Pharmaceutical and Medical Preparations Law No. 1262, facilities may store imported products and carry out secondary packaging activities for these products, provided that they employ a responsible manager pharmacist. **Therefore, in accordance with the current legislation, in order for the heading of "2.3.1 Facility for Physical Importation" to be applied, the facility responsible manager must be a pharmacist, among other conditions in the Regulation.**

2.3.2 Import of Semi-Finished Products to be Additionally Treated

The type of intermediate product to be imported should be specified in detail.

e.g.: granule, sterile active substance, partially manufactured biological product

2.3.3 Biological Active Substance
2.3.4 Other (Clarify)

Any restrictions or clarifying remarks related to the scope of this certificate *:

Explanations or restrictions on the activities carried out at the facility should be stated in this section. If the explanation or restriction is limited to a specific activity or dosage form, the number of the relevant heading shall be indicated.

Special Requirement Table

In case there are dosage forms manufactured at the facility that require special requirements, select the relevant special requirement and specify the dosage forms in the box.

Unless otherwise stated in the Restriction/Explanation section, a facility that manufactures a dosage form with special requirements may also manufacture products of the same dosage form that do not have special requirements.

Contract Facility Form

In the event that a service within the scope of manufacturing activity is procured from the Agency or from another facility authorized by the relevant authority of the country where it is located, as a part of the manufacturing activities carried out in the facility at a manufacturing facility with a manufacturing site permit from the Agency, the information on the facility where the contracted service is received and the services received shall be specified in Annex-3.

Regarding the facilities included under Annex-3, at least part of the production must be carried out at the facility. If all production stages of the products for which the company has authorization are carried out by contract manufacturing at another facility with permission from the Agency, and no stage of production (lot release, secondary packaging etc.) of these products is carried out in the manufacturing facility belonging to the company holding the marketing authorization, this situation does not fall within the scope of Annex-3.

8.1.4 Supplementing Documentation Checklist and Warnings

- Upload each document in the list that you have marked to the electronic system in a complete, legible and, if possible, searchable pdf format.
- The signing date of the application form should not be older than 6 months.
- The eye report requested for the responsible manager pharmacist must be prepared by a specialist ophthalmologist. The report should not be older than 6 months.
- It is sufficient for the health report requested for the responsible manager to be an individual physician report stating the health situation. The report should not be older than 6 months.
- Health reports should be prepared in the form of a physician report reporting the health situation, and analysis, examination, etc. results do not replace such report and the analysis/examination results do not need to be submitted.
- The facility master file must be uploaded to the system in one piece pdf format.
- Documents that should be original, notary/Agency approved or wet-signed according to the nature of the document must be original, notary/Agency approved, wet signed etc. and only be submitted electronically.
- The activity information indicated in the facility opening and operating permit must be **compatible with the activities to be carried out at the facility**. For instance, the permit of a facility that will carry out medicinal product manufacturing activities should not be limited to storage activities only, instead it should be stated in the activity information in the permit that medicinal product manufacturing activities will be carried out at the facility.
- The EIA decision must be made in accordance with the activities to be carried out at the facility.

8.2 Permit Document

In order to be able to issue a Manufacturing Site Permit on behalf of the **facilities that were found in compliance** in result of the opening application, or the manufacturing site permit certificate in case of loss due to reasons such as loss, fire etc., an application must be made to the Agency.

In cases where the facility is also lost, such as a fire, a permit shall be issued after the facility makes a new application for opening and proves relevant compliance.

Therefore, in order to apply for the permit, initially the opening application must be made and the relevant approval must be obtained in result of the inspection carried out at the facility.

8.2.1 Permit Document Application

- An application shall be made to the Agency in the following document types via EAS with the cover letter regarding the request for the manufacturing site permit and the accompanying documents, if any;
    - **a.** *"Traditional Herbal Medicinal Product Production Site Permit"* for facilities only dealing in traditional herbal medicinal products
    - **b.** *"Allergen Products Manufacturing Facility Permit Document"* for allergen products manufacturing sites,
    - **c.** For other facility types, "Medicinal Product / Dietary Food for Special Medical Purposes / Central Radiopharmacy Laboratory / Homeopathy Manufacturing Facility Permit"
- The application made in the correct document type shall be approved and an accrual shall be created for the payment.
- Following the payment of the document fee, the process of issuing the permit document shall be started.
- The issued permit document shall be sent to the applicant.
- The facility title, address, date and number of the permit, and a copy of the permit shall be published in the "Domestic Facilities Permitted by Our Agency" field on the website of the Agency.

8.3 Additional Activity

In the event that an additional activity is desired to be carried out in a permitted facility to the already approved activities in the permit, or major changes/modifications are to be made in the existing fields of activity or equipment, initially an application must be made to the Agency and if the said activity is deemed appropriate by the Agency, the additional activity may be initiated.

- Creation of a new production area within the scope of capacity increase and/or relocation of the production area within the facility,
- Major equipment change, while not changing the production area,
- Major changes to the ventilation system,
- Major changes to the water system,
- Major changes to compressed air, steam, other gases, etc. systems

Are evaluated within the scope of additional activities.

For the changes that are not classified as major, an application is made to the Unit with the document type "Other Changes at the Manufacturing Site**". As a result of the evaluation to be made, if deemed necessary, the applicant is notified to apply for an additional activity audit.**

8.3.1 Additional Activity Application

- For the changes that are not classified as major, an application is made to the Unit with the document type "Other Changes at the Manufacturing Site".

  For major changes the procedure is as below;

- Apply to the Agency in the appropriate document type, with a cover letter, *Additional Activity Application Form* and supplementing documents within the scope of the legislation.

  a. *For facilities* of which field of activity comprises solely of traditional herbal medicinal products*, an application in the document type "Traditional Herbal Medicinal Product Manufacturing Site Additional Activity Inspection" shall be required.*

  b. For facilities of which field of activity comprises solely of analysis activities based on lot release of finished products, an application in the document type *"Medicinal Products for Human Use Contract Analysis Laboratories Additional Activity Inspection"* shall be required.

  c. For allergen products manufacturing sites, an application in the document type *“Allergen Products Manufacturing Facility Additional Activity Inspection” shall be required.*

  d. For all other facilities*, an application shall be made in the document type "Medicinal Product/Dietary Food for Special Medical Purposes/Central Radiopharmacy Laboratory/Homeopathy Manufacturing Facility Additional Activity Inspection".*

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- Fill in the additional activity application form completely in digital environment.
- Upload the necessary supplementing documents such as change inspection form, risk assessment report, validation report, qualification report, sketch and facility plan to the

system as attachment to the application, regarding the additional activity to be carried out, together with the application form.

- After the application reaches the Agency, the documents pertaining to the application shall be evaluated by the Agency and any deficiencies, if any, shall be notified in writing.
- In case of deficiencies, complete the relevant deficiencies and repeat the application. This process shall be repeated until all deficiencies are eliminated.
- When no deficiency is detected in the application by the Agency or all the deficiencies reported are corrected by the applicant, the application shall be approved and an accrual shall be created for relevant payment.
- Following the payment of the inspection fee, the inspection planning process shall be initiated by the Agency.
- The result of the inspection report prepared in conclusion of the inspection carried out by the Agency inspectors shall be notified in writing to the applicant.
- Send the documents indicating that the shortcomings reported in result of the report have been completed to the Agency as specified in the Corrective and Preventive Action Document title.
- If an update is required in the permit following the letter of compliance at the end of the inspection process, apply as specified in the Permit Certificate Update title.

8.3.2 Filling in the Additional Activity Application Form

- Active substance manufacturing facilities are required to fill in the *Active Substance Manufacturing Form* for each new active substance to be manufactured within the scope of additional activity.
- Two separate forms must be filled for medicinal products for human use and investigational medicinal products for human use.
- In case new dosage forms are planned to be produced within the scope of additional activity, new dosage forms must be specified in the *4 Remarks* section.
- While specifying the dosage forms, the Pharmaceutical Dosage Form list should be taken as a basis and the main heading of the dosage form should also be stated.
- If contract service is to be outsourced from a new facility within the scope of the additional activity application, the Contract Manufacturing Facility form must also be filled for each facility from which service is to be received. (For instance, in case an application for additional activity is made for the production of a new dosage form while secondary packaging service is planned to be obtained from another facility for this dosage form)

8.4 Permit Document Update

In case of any change in the information and activities in the permit, the permit issued on behalf of the facility must be updated.

In case of one or more of the changes mentioned in this section, an application for updating the permit shall be required.

Remarks about the situations that require updating are included in In the table below in line with the section headings in the permit document.

Change in Company/Facility Information
Trade title change
In case the registered trade title of the company changes, the title in the document must be updated. Such change is only valid if the company title changes within the scope of the status amendment. In case the facility is transferred to another company etc., an opening application must be made instead.
Updating the permit holder address
In case the registered commercial center of the company is moved to another address or the central address in the document is updated by the municipality etc., the permit document must be updated.
Updating the factory address
In case the facility address is updated by the municipality, organized industrial zone administration etc., the address of the manufacturing site in the manufacturing site permit must also be updated. If the facility is **moved to another address**, address changes are not considered within the scope of document updating, in which case, **an opening application must be made again** for the new address where the facility will operate.
Changes to Section-1 and/or Section-2
Adding permitted activity
In the event an additional activity is to be carried out in addition to the activities permitted in the manufacturing site permit, initially an “Additional Activity Application” shall be made. The document update application must be made after the additional activity application is evaluated and approved by the Agency.
Terminating Permitted Activity
In case of termination of any of the existing permitted activities included in the manufacturing site permit, a document update application should be made in line with the applicant's declaration.

Changes in Information Indicated Under Annex-3
Adding a New Contract Manufacturing Facility
In case of outsourcing services for manufacturing activity from another facility in addition to the contract manufacturing facilities already included in the annex to the manufacturing site permit, an application for Permit Document Update should be made and the new facility details should be added to the facilities included under Annex-3. In case the facility for which the new contract is signed is approved by the Agency, the Permit Document shall be updated.
Cancellation of Approved Contract Manufacturing Facility
In the event that all services outsourced from any of the approved facilities included in the Manufacturing Site Permit are terminated, the relevant facility must be removed from the list in Annex-3 of the Manufacturing Site Permit.
Updating Approved Contract Manufacturing Facility Information
In the event that the address, title, etc. information of any of the facilities included in Annex-3 of the manufacturing site permit document changes, the permit document must be updated to include up-to-date information.
Updating Services Outsourced From Approved Contract Manufacturing Facility
In case of receiving services for one or more activities in addition to the activities specified in Annex-3 from an approved contracted production facility already included in Annex-3 of the manufacturing site permit, or canceling one or more of the services received, the permit document must be updated. Example 1: While receiving sterilization service from facility A, secondary packaging service has also been started to be outsourced. Example 2: While receiving sterilization and secondary packaging service from facility A, secondary packaging service outsourcing has been terminated.

8.4.1 Permit Document Update Application

- Within the scope of the legislation, apply to the Agency with a cover letter, *Permit Document Update Form* and supplementing documents, in the appropriate document type.
    - **a.** For facilities of which field of activity comprises solely of traditional herbal medicinal products, an application in the document type *"Traditional Herbal Medicinal Product Manufacturing Site Permit Document Update"* shall be required.
    - **b.** For allergen products manufacturing sites, an application in the document type "*Allergen Products Manufacturing Facility Permit Document Update*" shall be required.
    - **c.** For all other facilities*, an application shall be made in the document type* "Medicinal Product/Dietary Food for Special Medical Purposes/Central Radiopharmacy Laboratory/Homeopathy Manufacturing Facility Additional Activity Inspection".
- Send the original of the manufacturing site permit to the Agency as annex to the application in the appropriate document type.

- After the application reaches the Agency, the documents pertaining to the application shall be evaluated by the Agency and any deficiencies, if any, shall be notified in writing.
- In case of deficiencies, complete the relevant deficiencies and repeat the application. This process shall be repeated until all deficiencies are eliminated.
- When no deficiency is detected in the application by the Agency or all the deficiencies reported are corrected by the applicant, the application shall be approved and an accrual shall be created for relevant payment.
- Following the payment of the document fee, the old document shall be canceled and the current manufacturing site permit shall be issued.
- The updated manufacturing site permit shall then be sent to the applicant.
- The information about the manufacturing site permit shall be updated in the "Domestic Facilities Permitted by Our Agency" list in the Agency database and on its website.

8.4.2 Filling in the Permit Update Form

- In the permit update form, select the scope of the update. You may request updates for more than one heading in one application. For instance, if both the company's trade title and the address of the permit holder have changed and if there will be additions to the permitted activities, please tick all three relevant change headings in the application form.
- The supplementing documents that must be submitted for each change in the form are specified in the column next to the relevant heading. These documents must be submitted as annex to the application.
- In order for a new activity to be added to the manufacturing site permit, you must first apply for an Additional Activity and have received an approval letter from the Agency for the activity in question.

8.5 Responsible Manager Pharmacist Certificate

When the responsible manager pharmacist of the human medicinal product production facility permitted by the Agency changes or as a result of the approval of the opening application for the facility, an application must be made to the Agency for the appointment of the first responsible manager pharmacist.

In case of a change of responsible manager, the responsible manager pharmacist certificate that was previously issued on behalf of the former responsible manager shall be returned to the Agency and canceled, and a new responsible manager certificate shall be issued on behalf of the new responsible manager at the same time.

In accordance with the Regulation, a new responsible manager pharmacist must be appointed and an application must be made to the Agency within 30 days at the latest from the day the responsible manager leaves their position. **If no application is made to the Agency within the period specified in the Regulation, the facility activities shall be suspended in accordance with the eighth paragraph of Article 27 of the Regulation.**

In respect to the applications made for the issuance of a responsible manager pharmacist certificate for the facilities that received approval after the opening inspection, there is no need to send again the responsible manager pharmacist documentation submitted to the Agency within the opening application dossier file.

Pursuant to Article 9 of the Regulation;

The responsible manager has to have graduated from at least one of the branches of pharmacy, medicine and chemistry that provides at least four years of undergraduate education.

Provided that they fulfill the conditions specified in the Regulation, the manufacturing site permit holder may undertake the responsibility of responsible manager pharmacist by themselves.

The responsible manager pharmacist must certify that they have at least two years of practical experience in one or more of the manufacturing, quality assurance or quality control activities in one or more manufacturing sites that have been given a manufacturing site permit by the Agency or the authority of the country where they are located, with **social security premium documents and the employer's statement**.

However, the experience requirement is not sought for the members of the professions mentioned in the first paragraph of the Regulation **who also have a doctorate degree in related fields**.

The provision referred to in Article 5 of the Law No. 1262 is applied to the responsible manager candidates of the Quality Control Laboratories that make application to carry out analysis activities based on batch release of finished products.

8.5.1 Responsible Manager Pharmacist Certificate Application

- Within the scope of the legislation, apply to the Agency with a cover letter, *Responsible Manager Pharmacist Certificate Application Form* and supplementing documents, in the appropriate document type.

    a. For facilities of which field of activity comprises solely of traditional herbal medicinal products, an application in the document type *"Traditional Herbal Medicinal Product Manufacturing Site Responsible Manager Pharmacist Certificate"* shall be required.

b. For Allergen products manufacturing sites, an application shall be made in the document type "*Allergen Products Manufacturing Facility Responsible Manager Pharmacist Certificate*"

c. For all other facilities, an application shall be made in the document type "*Medicinal Product/Dietary Food for Special Medical Purposes/Central Radiopharmacy Laboratory/Homeopathy Manufacturing Facility Responsible Manager Certificate*".

- If there is a change of responsible manager pharmacist, please attach the original of the responsible manager certificate, which belonged to the former responsible manager whose duty has ended, to your application file.
- After the application reaches the Agency, the documents pertaining to the application shall be evaluated by the Agency and any deficiencies, if any, shall be notified in writing.
- In case of deficiencies, complete the relevant deficiencies and repeat the application. This process shall be repeated until all deficiencies are eliminated.
- When no deficiency is detected in the application by the Agency or all the deficiencies reported are corrected by the applicant, the application shall be approved and an accrual shall be created for relevant payment.
- Following the payment of the document fee, the certificate belonging to the former responsible manager shall be canceled and a new responsible manager certificate shall be issued for the responsible manager candidate.
- The issued responsible manager certificate shall be sent to the applicant.

8.5.2 Filling in the Responsible Manager Pharmacist Certificate Application Form

- Responsible manager pharmacist candidate must be graduated from pharmacy, medicine or one of the branches of chemistry providing at least four years of undergraduate education in accordance with Article 9 of the Regulation.
- The employer's statement and social security statements regarding the 2 years of practical experience of the responsible manager candidate specified in the 3rd paragraph of Article 9 of the Regulation must be submitted to the Agency.
- In the employer's statement, the position that the responsible manager candidate has worked before must be specified. The statement in question must be taken from the workplace where the responsible manager candidate has gained experience.
- The appointment date should be stated in the letter, indicating that the responsible manager candidate has been appointed as the responsible manager pharmacist by the employer.

8.6 Responsible Manager Pharmacist Certificate Annotation

In case of any change in the information contained in the responsible manager certificate issued on behalf of the responsible manager in charge of the facility with permit from the Agency, an annotation application for the responsible directorate document should be made to the Agency in order to update the changed information.

The changes in the following aspects in the responsible manager certificate shall be evaluated within the scope of the annotation application;

- Company title
- Facility address
- Responsible manager pharmacist name surname

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8.6.1 Responsible Manager Pharmacist Certificate Annotation Application

- Please apply to the Agency in the document type *"Traditional Herbal Medicinal Products Manufacturing Facility Responsible Manager Pharmacist Certificate Annotation Application"* for the facilities of which field of activity covers only traditional herbal medicinal products, "*Allergen Products Manufacturing Facility Responsible Manager Pharmacist Certificate Annotation*" for allergen products manufacturing sites and *"Medicinal Product / Dietary Food for Special Medical Purposes / Central Radiopharmacy Laboratory / Homeopathy Manufacturing Facility Responsible Manager Pharmacist Certificate Annotation Application*" for all other facilities, together with the original of the responsible manager certificate and the supplementing documents regarding the change.
- A copy of the trade registry gazette stating the change of title- in the case of change of company title,
- The letter to be received from the Municipality/OIZ etc., indicating that the facility address has been changed -in the case of change of facility address,
- Supplementing documents such as court decision showing the decision of change -in the case of change of the responsible manager pharmacist name/surname, should be submitted to the Agency.
- After the application reaches the Agency, the documents pertaining to the application shall be evaluated by the Agency and any deficiencies, if any, shall be notified in writing.
- In case of deficiencies, complete the relevant deficiencies and repeat the application. This process shall be repeated until all deficiencies are eliminated.
- When no deficiency is detected in the application by the Agency or all the deficiencies reported are corrected by the applicant, the application shall be approved and an accrual shall be created for relevant payment.
- Following the payment of the document fee, the necessary annotation shall be made on the responsible manager certificate.
- The annotated responsible manager certificate shall be sent to the applicant.

8.7 Responsible Manager Pharmacist Authorization and Proxy Information

During the periods when the responsible manager is not on duty temporarily and is on leave, a proxy with the same qualifications to act as their substitute shall be appointed by the manufacturing site permit holder.

In the event that the responsible manager pharmacist's temporary absence from duty exceeds 30 days, the Agency shall be informed about the proxy to be made.

In the event that the duration of the mandate for the responsible manager pharmacist exceeds six months, an application must be made immediately to the Agency for the appointment of a new responsible manager.

The person who will act as proxy of the responsible manager must be an employee of the facility in question.

The responsible manager pharmacist proxy application is not valid in cases where the responsible manager resigns from their position. In case of resignation of the responsible manager, a new responsible manager pharmacist shall be appointed immediately.

8.7.1 Responsible Manager Pharmacist Authorization and Proxy Information Application

- With a cover letter stating that the responsible manager cannot be on duty temporarily / is on leave, apply to the Agency via the EAS in the document type *"Responsible Manager Pharmacist Authorization and Proxy Information"*.
- In the application, be sure to specify the time period for which the person who will act as proxy of the responsible manager will maintain such duty.
- In the annex of the application, submit the resume and current social security breakdown of the person who will act as proxy to the Agency electronically.
- After the application reaches the Agency, the documents pertaining to the application shall be evaluated by the Agency and any deficiencies, if any, shall be notified in writing.
- In result of an application sent in full, the proxy notification shall be recorded in the Agency's records.

8.8 Good Manufacturing Practices Certificate

Manufacturing License and Good Manufacturing Practices (GMP) Certificate shall be issued by the Agency on behalf of the authorized facility manufacturing medicinal products for human use, in accordance with the activities included in the permit and upon the request of the facility authorities.

In the certificates to be issued, the **most recent general inspection** carried out at the facility by the Agency shall be taken as basis.

The Agency shall announce the current Manufacturing License and Good Manufacturing Practice (GMP) Certificate formats on its website. The Good Manufacturing Practice (GMP) Certificate format shall be determined by the applicant. Certificate may not be issued for any activity not included in the manufacturing site permit.

Manufacturing License and Good Manufacturing Practices (GMP) Certificate may be issued more than once at different times and in Turkish and/or English language upon the request of the applicant.

8.8.1 Good Manufacturing Practices Certificate Application

- Apply to the Agency with the drafts of certificates you request to be issued and relevant cover letter, with the document type *"Manufacturing License"* or *"GMP Certificate (Turkish and English - for Domestic Production Facilities)"*.
- In the cover letter, clearly indicate the certificate format(s) you request and the number of certificates.
- If you request an English certificate, please submit the English translation of your permit document as annex to the application.
- If you request a Manufacturing License, prepare a copy of the certificate and submit it in a searchable pdf format as annex to the application.
- After the application reaches the Agency, the documents pertaining to the application shall be evaluated by the Agency and any deficiencies, if any, shall be notified in writing.
- In case of deficiencies, complete the relevant deficiencies and repeat the application. This process shall be repeated until all deficiencies are eliminated.
- When no deficiency is detected in the application by the Agency or all the deficiencies reported are corrected by the applicant, the application shall be approved and an accrual shall be created for relevant payment.
- Following the payment of the document fees, the certificate(s) issued by the Agency shall be sent to the applicant.

8.9 Corrective and Preventive Action Documentation

Corrective and preventive action documents (CPA) indicating that the deficiencies, identified in the facility in result of the inspection carried out by the Agency inspectors, are eliminated must be submitted to the Agency within the time period notified to the company following the notification of the inspection result.

8.9.1 Corrective and Preventive Action Documentation Application

- Make an application in the *"Corrective and Preventive Action Document"* document type on the EAS with the documents stating that the deficiencies communicated in writing by the Agency have been corrected.
- Keep the letter of the report results sent by the Agency as reference to your application in the system and in the cover letter.
- After your application is completed, the documents submitted shall be evaluated by the Agency inspectors.
- The result of the evaluation of the inspectors shall be notified in writing by the Authority.
- If it is concluded as a result of such evaluation that the deficiencies have not been corrected and additional documents are requested, the above process is repeated.

8.10 Facility Master File

All facilities with a manufacturing site permit are required to prepare the facility master file, which includes information on the activities carried out in the facility and on the quality management system, and submit it to the Agency for registration.

It is essential that the facility master file is submitted to the Agency during the opening application, but facilities that have not yet prepared the facility master file at the application stage are allowed to submit their facility master files to the Agency after obtaining the permit.

In case of changes in the facility master file, the current facility master file shall be submitted to the Agency, and the facility's master file shall be updated in the electronic database by the Agency.

The facility master file application is only within the scope of updating the facility master file in the Agency's electronic database, and does not mean that the change made in the facility is approved. If the updated sections in the facility master file require a separate application within the scope of this guidelines document, the relevant application must also be made and relevant approval must be obtained.

8.10.1 Facility Master File Application

- In case of any changes and updates in the facility master file, apply in the "Facility Master File" document type with relevant cover letter and the current facility master file.
- Submit the facility master file to the Agency electronically in one piece and in pdf format.
- The facility record shall be updated in the Agency database and the facility master file shall be accordingly recorded.

8.11 Inspection Book

All facilities for which a manufacturing site permit has been issued must procure an inspection book approved by the Agency in order to be available for the inspections to be carried out at the facility.

The inspection book application should be made after the manufacturing site permit is issued to the facility.

8.11.1 Inspection Book Application

- Please apply to the Agency in the document type of *"Domestic Facility Inspection Book"* with relevant cover letter stating your inspection book request.
- The application made in the correct document type shall be approved and an accrual shall be created for the payment.
- Following the payment of the document fee, the process of issuing the inspection book shall be started.
- The prepared inspection book shall then be sent to the applicant.

8.12 Key Personnel Change

Pursuant to Article 8 of the Regulation, it is obligatory to employ a production manager, a quality assurance officer, a quality control officer and adequate number of appropriate personnel who have received appropriate training and sufficient experience, together with the responsible manager pharmacist.

Apart from the change of responsible manager, the Agency should also be informed about any changes to the key personnel mentioned.

8.12.1 Key Personnel Change Application

- Please apply in the document type *"Change of Key Personnel at Manufacturing Site (Excluding Responsible Manager Pharmacist)"* with an explanatory cover letter for the change in key personnel.
- The resume of key personnel, undergraduate diploma or school exit certificate, letter stating acceptance of duties and responsibilities, other documents pertaining to duties and professional experience, and an updated organizational chart shall be presented in the application annex.
- A application made in full shall be registered in the records of the Agency.

8.13 Foreign Authority Inspection

In case a licensed manufacturing facility is requested to be inspected by another country authority, the scope of the said inspection and the information of the authority that will carry out the inspection must be reported to the Agency prior to the inspection.

If deemed necessary, the Agency may also participate in the inspection in question. If major or critical findings that may affect the GMP level of the facility are detected as a result of the inspection, the Agency should be informed by the facility authorities.

8.13.1 Abroad Authority Inspection Application

- Please apply in the *"Facility Inspection by Foreign Authorities"* document type, together with the cover letter containing the scope of the inspection planned by the foreign authorities, the date of the inspection and the information of the authority to perform the inspection.
- The application shall be taken into the records of the Agency and, if necessary, relevant plans shall be made by the Agency for participation in the inspection.

8.14 Facility Closure

In the event that all activities of the manufacturing facility are terminated by the Agency or facility officials, or that the facility is closed as a result of a disaster etc., relevant application should be made to the Agency the facility's manufacturing site permit, responsible manager pharmacist certificate and GMP certificate should be canceled. Documents pertaining to these processes may also be sent to the Agency through Provincial Directorates of Health.

8.14.1 Facility Closure Application

- Apply to the Agency, by using the *"Facility Closing Procedures"* document type, together with the cover letter stating that the facility is closed and all its activities are terminated by the facility authorities, the minutes issued by the Provincial Directorate of Health stating that the facility is not operating at the relevant address, the manufacturing site permit and the originals of the responsible manager certificates via EAS.
- You may also submit the documents pertaining to this process to the Agency through the Provincial Directorate of Health.
- If a deficiency is detected in the information and documents in the evaluation made by the Agency, such deficiency shall be notified to the applicant.
- In case of a deficiency, repeat the application by completing the missing documents.
- If the Agency does not detect any deficiencies in the information and documents in the application, or if all the deficiencies are corrected, the manufacturing site permit issued in the name of the facility, good manufacturing practices certificates and the responsible manager pharmacist certificate shall be cancelled.
- The applicant shall be notified of the cancellation of the aforementioned documents through the Provincial Directorate of Health.

- Information about the manufacturing facility shall be removed from the "Domestic Facilities Permitted by Our Agency" list on the website of the Agency.
- In the event you want to commence operations again after the documents are cancelled, you must make an opening application.

9 FACILITY INSPECTIONS

9.1 Types of Inspections

The inspections carried out by our Agency within the scope of the current legislation are classified as follows.

- Opening / Additional Activity Inspections
- Follow-Up Inspections
- General (Routine) Inspections
- Special Inspections

In order to use the workforce and time effectively in the inspections conducted by the Agency, more than one type of inspection may be performed during an inspection visit.

Opening / Additional Activity Inspections

These are the inspections conducted for the facilities that are to commence operations for the first time *(opening inspection)* or in case an operating facility is willing to carry out a new activity *(additional activity inspection)* in response to the applications made by manufacturing facilities. The scope of the inspection is limited to the application. Details on the principles of application for the said inspections are included under the headings 8.1. Opening and 8.3 Additional Activity.

Follow-Up Inspections

These are the inspections made in cases where the deficiencies detected in any inspection conducted at the facility necessitate an on-site inspection at the facility.

General (Routine) Inspections

These are the inspections carried out at certain intervals in line with risk-based inspection planning to determine that the facility with a manufacturing site permit document maintains its compliance with the GMP Guidelines. The maximum general inspection period is 3 years and there is no need to apply to the Agency for general inspection planning. In general inspections, all manufacturing activities in the facility are inspected. In such inspection to be carried out, the following issues are evaluated;

- Whether the facility is operating in accordance with the legislation in force
- Whether compliance with the standards continues in accordance with the current GMP Guidelines
- Whether the activities carried out are in compliance with the manufacturing site permit

Special Inspections

In cases where there is doubt about GMP compliance in permitted facilities, where there are significant complaints about the facility in terms of GMP, where the defects in products produced in

the facility and recalls require inspection etc., an on-site inspection may be conducted at the facility. These inspections may be carried out without notice.

9.2 Risk-Based Inspection Planning

General inspections are planned according to the risk-based inspection approach, and parameters such as the GMP level in the previous inspections of the facility, the risk level of the products produced in the facility (whether there is sterile production etc.), the presence of significant complaints in terms of GMP, and the time elapsed since the last general inspection shall all be taken into consideration. Facilities that have been granted a manufacturing site permit in conclusion of the opening inspection may be included in the general inspection plan in the year following the year in which the facility was granted permit, in line with risk-based inspection planning. The maximum general inspection period for all facilities is 3 years, except in extraordinary circumstances.
Findings detected in the inspections conducted by the Agency are classified as critical shortcomings, major shortcomings and other shortcomings.

Critical shortcomings: Shortcomings that will result in the emergence of a product that harms/has the risk to harm human health.

Major shortcomings: A non-critical shortcoming that causes or may result in a product that does not match the information presented in the registration application, a shortcoming that causes a major deviation from PIC/S good manufacturing practices, a shortcoming that indicates a major deviation from the considerations specified in the manufacturing site permit, a shortcoming that may result in a failure to implement the necessary procedures for lot release or that indicate that the authorized persons are not performing their duties, shortcomings that are not major in themselves but, when combined with many further 'other shortcomings', represent a major shortcomings and are disclosed and reported as such.

Other shortcomings: Shortcomings that cannot be classified as critical or major but indicate a departure from good manufacturing practices.

The GMP compliance level of the facility is determined according to the table below, taking into account the findings of the general inspection of the facility and the general condition of the facility.

GMP Compliance Level Table

Acceptable Compliance	
Good	Good compliance with GMP Guidelines There may be some shortcomings at another level. There should be no critical or major shortcomings.
Satisfactory	Moderate compliance with GMP Guidelines Some shortcomings in the major category (not one critical finding) (1 to 5 major)
Minimum Requirement	Limited compliance with GMP Guidelines Some shortcomings (no critical finding) in the relatively more serious category of major, more than 5 major shortcomings.

Unacceptable Compliance	Unsatisfactory GMP compliance standard with one or more critical findings and/or multiple major findings indicating that the company's quality management system is not working well. Significant risk of substandard and/or unsafe products being produced

The risk levels of the licensed facilities are determined as follows in conclusion of the results of the inspections conducted at the facilities, the activities carried out at the facilities and the evaluations made by the Agency.

High risk category
Sterile product facilities with recall processes, facilities with parametric release, facilities with biological processes etc.
Facilities with significant complaints under GMP etc.

Medium risk category
Non-sterile product manufacturing facilities with recall processes
Sterile product manufacturing facilities and facilities performing parametric release, facilities carrying out biological processes etc.

Low risk category
Non-sterile production facilities, medical gas facilities, secondary packaging facilities etc. where the aforementioned conditions are not valid and there is no change or problem related to quality

Risk-based audit planning is made in accordance with the table below in conclusion of the inspections carried out at the permitted facilities, the risk levels of the facilities and the evaluation made by the Agency.

Inspection Frequency Table (Values are shown on a monthly basis.)

Risk Category	**Acceptable Compliance**			**Unacceptable Compliance**
	Good	Satisfactory	Minimum Requirement	
High	**24**	**24**	**12**	The decision shall be made based on the facts of the case.
Medium	**36**	**24**	**12**	The decision shall be made based on the facts of the case.
Low	**36**	**36**	**12**	The decision shall be made based on the facts of the case.

9.3 Post-Inspection Processes

For the facilities of which GMP compliance is at an "unacceptable level" as per the inspections carried out by the Agency, manufacturing site permit/GMP certificate shall not be issued for the opening inspection, and if the facility is already in operation, the facility activities shall be suspended.

If any issues are detected during or after the inspection falling within the scope of the provisions under Articles 18, 19 or 20 of the Pharmaceutical and Medical Preparations Law No. 1262, the relevant administrative fines specified in the aforementioned Law shall be implemented by the Agency.

Furthermore, in accordance with the provisions specified in Article 27 of the Regulation, the manufacturing site permit and the responsible manager pharmacist certificate of the facilities that are found to be operating in violation of the Regulation may be suspended completely or partially.

10 CHANGES THAT MUST BE NOTIFIED BY MANUFACTURING FACILITY OWNERS

Facilities with a manufacturing site permit must notify the Agency of any changes to be made regarding the manufacturing site before the changes are put into practice. In case the changes to be made regarding the manufacturing site are of such a nature that they may affect the details defined in the manufacturing site permit, pre-approval must be obtained from the Agency before the implementation of the relevant change. In addition, pre-approval must be obtained from the Agency before the implementation of some changes that will take place for the permitted activities defined in the manufacturing site permit.

Below is the summary table indicating the administrative and technical classification of the notifications of changes to be made to the Agency and under which heading in the Guidelines the application should be made within the scope of the changes.

Table of Changes to be Notified by Manufacturing Site Owners

Change	Form of Evaluation	Risk Assessment	Application Scope
Transfer of facility	Technical	High	8.1 Opening
Transfer of facility ownership	Technical	High	8.1 Opening
Additional changes to approved manufacturing activities	Technical	High	8.3 Additional Activity
Major changes in the field and/or equipment related to manufacturing processes in the facility	Technical	High	8.3 Additional Activity
Changes related to auxiliary units in the facility	Technical	High	8.3 Additional Activity

Other changes that are not major made at the facility	Technical	Medium	8.3 Additional Activity
Planning the manufacture of products other than medicinal products for human use in the facility within the scope of Article 7 of the Regulation	Technical	Medium	Application must be made within the scope of ***the Guidelines on Applications for Risk Assessment of Facilities Manufacturing Medicinal Products for Human Use.***
Typographic errors/minor corrections in the facility permit document	Administrative	Low	8.4 Permit Document Update
Change in the permit holder's title	Administrative	Low	8.4 Permit Document Update
Change in the permit holder's address	Administrative	Low	8.4 Permit Document Update
Typographic change in the address of the manufacturing facility	Administrative	Low	8.4 Permit Document Update
Removal of an approved manufacturing activity(s) from a document	Administrative	Low	8.4 Permit Document Update
Addition/removal of contract manufacturing facility	Administrative	Low	8.4 Permit Document Update
Change in the title of the contract manufacturing facility	Administrative	Low	8.4 Permit Document Update
Change in services outsourced from contract manufacturing facility	Administrative	Low	8.4 Permit Document Update
Responsible Manager Pharmacist changes	Administrative	Low	8.5 Responsible Manager Pharmacist Certificate
Typographic change in the responsible manager certificate	Administrative	Low	8.6 Responsible Manager Pharmacist Certificate Annotation

Permit/proxy notification regarding the responsible manager	Administrative	Low	8.7 Responsible Manager Pharmacist Authorization and Proxy Information
Key personnel changes other than responsible manager pharmacist	Administrative	Low	8.12 Key Personnel Change
Update of facility master file	Administrative	Low	8.10 Facility Master File
Inspection of the facility by foreign authorities	Administrative /Technical	Low	8.13 Foreign Authority Inspection

Applications in the low risk group are evaluated and finalized by the Unit within the scope of Administrative evaluation.

Applications in the medium risk group are evaluated and finalized by our Institution's Inspectors and/or BIRDEK commission within the scope of technical evaluation.

Applications in the high risk group are finalized by subjecting them to the inspection of our Institution's Inspectors within the scope of technical evaluation.

11 ANNEXES

- Opening Application Form
- Active Substance Facility Opening Application Form
- Active Substance Manufacturing Form
- Additional Activity Application Form
- Permit Document Update Form
- Contract Manufacturing Facility Form
- Responsible Manager Pharmacist Certificate Application Form
- Pharmaceutical Dosage Form List
- Manufacturing Site Permit Draft
- Responsible Manager Pharmacist Certificate Draft

12 COMMUNICATION

For your comments, suggestions and questions:

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Domestic Facility Inspections Application and Follow-Up Unit
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Vice Presidency of Inspectorate

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Söğütözü Mahallesi 2176.Sokak No:5 PK 06520 Çankaya/Ankara

13 EFFECTIVE DATE

This guideline enters into force on the date of approval.

With the entry into force of this Guidelines document***, the "Guidelines on Laboratories with Contract Analysis Services for Human Medicinal Products"*** and ***"Guide on Changes Required to be Notified by Manufacturing Site Permit Holders"*** have been repealed***.***

Revision History

Revision	Change	Effective Date
R.00	First publish	09.01.2022

R.01	The application titles were updated by adding the document types of the allergen products manufacturing facilities. The definition of secondary packaging facility has been updated to include also facilities that only carry out storage activity of human medicinal products and/or human medicinal products. The principles regarding the requirements of the responsible manager and key personnel have been added to the applications for quality control laboratory facility types. The procedure for notifying the Agency of non-major changes realized at the facility is explained under the title of Additional Activity. Changes to be reported by plant owners were classified according to the risk assessment.	