

**REPUBLIC OF TURKEY
MINISTRY OF HEALTH
General Directorate of Pharmaceuticals**

**LICENSING REGULATION
FOR
PHARMACEUTICAL
PRODUCTS**

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LICENSING REGULATION FOR PHARMACEUTICAL PRODUCTS

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PART ONE

Purpose, Scope, Legal Basis and Definitions

PURPOSE

Article 1. The purpose of this Regulation is to specify principles and rules to be adopted in licensing procedures as well as the practices in connection with licensed medical products intended for use in humans to ensure sufficient efficacy, necessary safety and the appropriate quality.

SCOPE

Article 2. This Regulation covers all medical products, either manufactured or imported, and all real and legal persons who apply and / or are granted licenses for such products.

LEGAL BASIS

Article 3. This Regulation has been prepared on the basis of the Human Pharmaceutical and Medical preparations Code No : 1262, the third article of the Basic Code on Public Health Services No : 3359 and the 43rd article of the decree in lieu of code on the organization and functions of the Ministry of Health.

DEFINITIONS

Article 4. Unless otherwise stated, within the framework of this Regulation :

a . Ministry : Refers to the Ministry of Health.

b . Registered Medical Product : Refers to medical products registered according to the code and this Regulation (to be) prepared ready for use and introduced in the market under a determined name and in a special package.

c . Medical Product : Refers to pharmaceutical and medical preparations containing natural and / or synthetic active ingredients or their combinations administered to humans to cure and / or prevent diseases, diagnose such diseases or cure, correct or change human physiological functions.

d . Active Ingredient : Refers to the materials contained in the desired therapeutic effect.

e . Inactive Ingredient : Refers to all materials contained in the composition of a medical product, excluding the ones creating the desired therapeutic effect.

f . Starting Materials : Refer to all kinds of materials used in production of a medical product except the packaging materials.

g . Package Material: Refers to all kinds of materials used in packaging the medical product except the ones used in transport and distribution.

h. Finished Product : Refers to the medical product that has been subjected to all manufacturing processes, ready for use in its final package.

i . Code : Refers to the Pharmaceutical and Medical Preparations Code No .1262.

j . Registration : Refers to the inspection and registration procedures carried out by the Ministry with the purpose of introducing a medical product into the market for therapeutic use.

k. Registration Certificate (Licence): Refers to the authorization granted for the manufacture of a medical product to be introduced into the market with a determined formula in a specific pharmaceutical form and dosage in accordance with the agreed product information.

PART TWO

Application, Evaluation and Licence

APPLICATION

Article 5. Legal and real persons intending to obtain a licence for a medical product are obliged to prepare and submit to the Ministry as an enclosure with their application petition all the information and documents shown in the Appendix as envisaged by this Regulation .

PERSONS AUTHORIZED TO MAKE LICENCE APPLICATIONS

Article 6. Below are given the qualifications sought pursuant to Article 5 of the Code in legal and real persons requesting a licence for introducing a medical product into the market:

- a . Real persons shall have a profession in any one of the medicine, pharmacy or chemistry disciplines and shall have the authority to perform his or her profession in Turkey.
- b . Legal persons shall employ a responsible person with the qualifications indicated in subarticle (a), having the qualifications sufficient to provide any information requested by the Ministry about their products.

Dentists having the authority to perform his / her profession in Turkey have the rights to apply for the registration of products used in Dentistry.

PERSONNEL AND PLANT CONDITIONS

Article 7. Persons who will be given a licence for the purpose of introducing a pharmaceutical product into the market, shall have at least one qualified personnel and shall have a building for storing and distributing the product to meet the conditions specified in Article 28.

DOCUMENTS THAT SHOULD BE SUBMITTED FOR APPLICATION

Article 8. Detailed and sufficient information and documents for the sections listed below shall be annexed to the application petition to the Ministry for the Registration of a medical product

1. Summary of the Dossier
 - A. Administrative Information
 - B. Summary of Product Characteristics (SmPC)
 - C. Supplementary Information on the Product and the Manufacturer.
2. Chemical, Pharmaceutical and Biological Information
 - A. Composition
 - B. Manufacturing Method
 - C. Controls for the Starting Material
 - D. Controls for the Intermediate Product
 - E. Controls for the Finished Product
 - F. Stability
 - G. Bioavailability / Bioequivalency
 - H. Other Information
3. Pharmacological - Toxicological Documents
 - A. Single Dose / Repeated Dose Toxicity

- B. Studies on Reproduction Function
 - C. Embryofetal and Perinatal Toxicity
 - D. Mutagenic Potential
 - E. Carcinogenic Potential
 - F. Pharmacodynamics
 - G. Pharmacokinetics
 - H. Local Tolerance (toxicity)
 - I. Other Information
4. Clinical Documents
- A. Clinical Pharmacology
 - B. Clinical Studies
 - C. Other Information

ABRIDGED APPLICATIONS

Article 9. Provided that the following conditions are documented and supported sufficiently it may not be necessary to submit with the application form the pharmacological and toxicological test results or clinical studies on the medical product .

a . If the product in question is completely identical to a product previously licensed by the Ministry (with proof that it has the same qualitative and quantitative composition, has the same pharmaceutical form, is administered via the same route, and if applicable, has the same Bioavailability).

b . If its active ingredient(s) are proved, with references to the published literature, to have a known activity, acceptable safety and established medical use.

In this case, the applicant shall submit previously published literature and information on the efficacy and safety of the medical product in question.

DIFFERENTIATED APPLICATIONS FOR THE REGISTERED ACTIVE SUBSTANCES

Article 10. In the event that the product for which licence is sought has the same active ingredient(s) as a previously licensed preparation but is to be used in a different indication , route and dosage , results of pharmacological and toxicological tests and / or clinical studies in connection with such application must be submitted as an appendix to the application form.

For new medical products containing active ingredients already known but not yet therapeutically used in combination at the time of the application, results of pharmacological and toxicological tests and clinical studies on such a combination must be presented. However, it may not be necessary to give such information for each ingredient separately.

RESPONSIBILITY OF THE APPLICANT

Article 11. All information about the product given in the licence application appendix must be true, tested and final. The applicant is responsible for the accuracy of the information and the documentation and for enforceability, repeatability and precision of the methods employed.

RETURN OF APPLICATION

Article 12. If the following conditions, upon first examination of the application appendices submitted to the Ministry for Registration, are encountered, the application shall be rejected and returned to the applicant due to noncompliance with the procedural requirements :

- a . The applicant does not bear the qualifications specified in the related applicable legislation and regulation.
- b . Appendices of the application are not prepared and l or presented in the format specified in this regulation.
- c . Incompleteness of the information and documents in the appendiY or incompatibility with the product.
- d . Unsuitability of the production site for the manufacture of the product.

CRITERIA FOR REGISTRATION

Article 13. Upon giving Registration license for a medical product, the criteria of the Ministry are as follows :

- a . Efficacy under proposed administration conditions shall be proved.
- b . Taking into account, different patient groups (due to age, sex, etc.), safety under the proposed administration conditions shall be proved.
- c . Introducing the medical product into the market shall be beneficial.
- d . The product shall have suitable technical and pharmacological specifications.
- e . Its price shall be reasonable.

EVALUATION OF THE APPLICATIONS

Article 14. In the evaluation of information and documents proving the effectiveness, safety and quality of the product and forming the basis for scientific and technological assessments the following are taken into account :

- a . Clinical studies and clinical - pharmacological investigations designed and carried out in order to determine the efficiency and safety of the product must demonstrate its efficacy and safety in the therapeutic indication and under normal administration conditions envisaged for the use of the product ;
- b . Demonstration of the pharmacodynamic effect of the product on humans does not verify its therapeutic potential effect alone ;
- c . Statements about the efficacy and safety of a medical product under normal administration conditions shall not be considered valid unless supported by scientific data ;
- d . Whether or not the data on the therapeutic efficacy and safety of the medical product are proved and verified by published studies of different researchers is important for the evaluation of the application ;
- e . In order to determine the practicability of the methods presented by the manufacturer for control of the medical product and to confirm the accuracy of the formulation of the medical product, the necessary laboratory analyses shall be conducted by the Ministry. Any controls that cannot be made by the Ministry itself shall be completed appropriately by the applicant upon request by the Ministry ;
- f . Sufficient and conclusive studies should be made confirming that the product complies with certain specifications during its shelf - life.

In the event that documents appended to the application form fail to give sufficient information on the medical product, further studies or more updated information may be requested from the applicant. If necessary, oral and / or written comments will be requested from the applicant.

Article 15. In the evaluation of the marketing licence applications for medical products with a special therapeutic indication (e.g. efficacy in rare and vitally important diseases),the applicant

can prove that detailed information on the efficacy and safety of the product under normal administration conditions cannot be supplied due to the following reasons :

- a . it is impossible for the applicant to present comprehensive proofs because of the extreme rareness of the indications of the relevant product,
- b . detailed information cannot be supplied within the framework of the present scientific data,
- c . gathering such information is contrary to general ethical rules, then a marketing licence shall be given, provided, however, that :

1.it is administered only through prescription and in some cases, it is used under strict medical control and / or in hospitals ;

2.package information and all other medical data on the product shall be worded to clearly state that sufficient information has not yet been gathered on certain aspects of the product.

REJECTION OF THE LICENCE APPLICATION

Article 16. If, upon evaluation of the documents annexed to the application form submitted to the Ministry, it is determined that :

- a .the preparation has harmful effects under normal administration conditions (if the potential risk is higher than the therapeutic effect) ,
- b .the therapeutic effect of the preparation is either insufficient or not appropriately proven,
- c .bioavailability of the preparation is insufficient (for applicable products) ,
- d .introduction into the market is not beneficial,
- e .the qualitative and quantitative compositions of the preparation are not exactly as stated in the application form,
- f . no result is reached upon application of the known control methods or the specifications continue to fail to comply with the declared acceptable limits after a second control although the applicant has previously been warned about this nonconformity,

The application shall be rejected.

NOTIFICATION AND OBJECTION

Article 17. If the licence application is rejected, the applicant shall be notified of the decision with reasons. The applicant has the right to object against the decision. If deemed necessary during the discussion of the objection, the applicant shall be allowed to give a written and / or oral explanation in defence.

ISSUE AND CONTENTS OF THE LICENCE

Article 18. Upon examination and evaluation of the information and documents submitted to the Ministry, a marketing licence shall be issued for those medical products which are found to comply with the stipulations contained in this Regulation.

As accepted by the Ministry, this licence shall indicate the name of the product, its pharmaceutical form, dosage, packaging type, package quantity, route of administration and shelf-life and the name of the person responsible for the production or importation and / or marketing of the product, the name of the manufacturer, prescription /nonprescription sales status and the date and number of Registration.

LEGAL SALES CONDITIONS

Article 19. At the time the medical product is granted a licence, it shall also be decided whether it should be sold with or without prescription.

Products meeting the criteria listed below shall be licensed as prescription products, which will be sold only with prescription :

- a . products that may directly or indirectly pose a potential risk when used ; even if properly, without a physician's advice and control ,
- b . products that are often misused and have widespread use, thereby creating the possibility of direct or indirect harm to health,
- c . products considered requiring close follow - up due to their action and / or side effects,
- d . those requiring parenteral administration,
- e . those containing a substance classified as narcotic or psychotropic under international agreements.
- f . those having the potential for addiction if not used properly or those that may be used for illegal purposes ,
- g . those restricted to therapy under hospital conditions due to being a new entry, or with respect to public health.

In these evaluations, such items as single maximum dose and maximum daily dose, dosage regimen, and pharmaceutical form of the relevant product shall also be taken into account.

PRODUCTS SUITABLE FOR HOSPITAL USE

Article 20. Of the prescription products, those requiring use under hospital conditions shall bear a relevant notice printed in their packages.

CHANGING SALES CONDITIONS

Article 21. Upon evaluation and confirmation of newly published results, the Ministry may change the legal sales candidate of a product previously licensed for prescription or nonprescription sales. Such a change may be made any time when appropriate data or evidence are obtained as well as during the renewal of the product licence.

PRODUCTS SUBJECT TO SPECIAL PRESCRIPTION

Article 22. To determine whether products containing a substance determined to be narcotic and / or psychotropic under international agreements will be subjected to special prescription procedures set by the Ministry this shall be established by considering their addictive potential and abuse risks as well as their formulations and quantity of the related substance per dose and per pack.

If a medical product is decreed to be sold with special prescription, this fact is stated in its license.

VALIDITY OF MARKETING LICENCES

Article 23. Validity of marketing licences issued by the Ministry for medical products is five (5) years , which may be extended for five year periods if found appropriate upon the inspections carried out by the Ministry pursuant to Article 24. For licence renewal , the licensee must submit an application to the Ministry at least six months prior to the expiry of the licence.

Marketing licences for which no renewal application is made before expiry thereof shall be canceled by the Ministry.

REVIEW OF THE LICENCED PRODUCT

Article 24. Summary of Product Characteristics (SmPC) on the licensed pharmaceutical products shall be reviewed for efficacy and safety within the framework of the updated literature, announcements by national and international authorities, results of scientific studies and measures taken by health authorities. As a result of such a review, if deemed necessary, the Ministry may :

- a . allow the licensee to continue marketing of the product,
- b . request the licensee to rearrange or amend the SmPC,
- c . cancel the marketing licence of the product.

SUSPENSION OF MARKETING LICENCE

Article 25. The marketing licence of the pharmaceutical product shall be suspended by the Ministry if;

1. harmful effects have emerged under normal administration conditions ,
2. it is confirmed that the product has no therapeutic effect (therapy does not elicit any response) ,
3. it is manufactured using a different formulation from that declared in the licence ,
4. the formulation , dosage , pharmaceutical form , package , and prescribing information , on which the licence is based , are modified without prior knowledge and approval of the Ministry,
5. the necessary controls on the finished product are not being conducted , though included in the licence application ,
6. the control methods have not been updated in accordance with accepted techniques and standards ,
7. defective production is repeated ,
8. the licensee fails to comply with the Ministry's directives and warnings about the product ,
9. the address of the licensee can not be found ,
10. it is established that other provisions set by law and regulations concerning the production site and product are not strictly followed.

CANCELLATION OF MARKETING LICENCE

Article 26. The marketing licence of the medical product shall be canceled by the Ministry if :

1. the product is determined to be harmful under normal administration conditions,
2. it has no therapeutic effect,
3. the licensee voluntarily ceases manufacture,
4. license renewal is not applied for although the current licence is no longer valid,
5. the licensee has not responded within a maximum of six months about the product for which the licence is suspended for other reasons.

CESSATION OF MANUFACTURE

Article 27. If the licence of a product is suspended and/or canceled , its manufacture shall be stopped. The decision on the inventories already in distribution and sales channels shall be at the discretion the Ministry, taking into account the rationale of license suspension and / or cancellation.

RESPONSIBILITY OF THE LICENSEE

Article 28. With respect to the licensed medical products, the licensee is responsible the Ministry to assure that :

- a . the product is manufactured in accordance with the Ministry-approved specifications given in the appendix to the application form,
- b . the manufacturer regularly and properly applies the necessary controls on the product,
- c . the technical and scientific developments are monitored closely so that any modifications allowing the product test to be conducted with generally accepted scientific methods are made in a timely fashion ,

- d . the insert information of the preparation is updated for safe and accurate administration of the product,
- e . any changes in the composition, pharmaceutical form, package, shelf life and insert of the product are advised to the Ministry together with reasons and supporting documents before they are implemented,
- f . the Ministry is advised of any changes in the manufacturing process and test methods with reasons for such change and results of validation studies, if necessary,
- g . the Ministry's questions on the product are answered (within a reasonable time),
- h . the product's efficacy, safety and quality are monitored and the findings are evaluated following introduction of the product into the market,
- i . the requirements of the regulatory rules set by the Ministry for pharmaceutical products are strictly met.

ANNOUNCEMENTS

Article 29. Names of medical products which are licensed and whose marketing licence is canceled by the Ministry shall be announced in the Official Gazette together with the name of the licensee and licence number.

PART III Manufacture and Sales

PREMISES

Article 30. Medical products shall be manufactured only at sites permitted by the Ministry. It must also be acknowledged and confirmed by the Ministry that the manufacturer owns sufficient premises, equipment, personnel and technology and laboratory facilities to ensure that the specified form of the relevant preparation will be produced and controlled in accordance with "Good Manufacturing Practice" (GMP).

For products manufactured abroad:

- a. an official document certifying that the manufacturer is authorized to manufacture the relevant product in the country of origin, and
 - b. a document certified by the official authorities verifying that the manufacturer carries out its production activities in accordance with Good Manufacturing Practice (GMP) and is inspected as and when necessary,
- must be attached to the application form.

The Ministry may, if deemed necessary for inspecting the quality of the product, visit the manufacturer's premises abroad and inspect the manufacturing and control activities on site. Such inspection shall be advised to the manufacturer as well as the official authorities of that country prior to such visit.

THIRD- PARTY PRODUCTION / CONTROL

Article 31. In the event that the applicant is not the manufacturer of the medical product, a third-party production agreement executed between the applicant and a third-party manufacturer bearing the qualifications stated in Article 30 shall be attached to the application. If certain phases of the manufacturing process or some of the control procedures take place at another site, this will be indicated in the application form. Such sites are subject to the approval of the Ministry. The agreement made with production and / or control sites and specifying obligations of each party must be attached to the application form.

MANUFACTURING UNDER LICENCE

Article 32. Applicants intending to obtain a licence for a medical product already licensed abroad in the name of a foreign company shall submit to the Ministry, together with the information and documents required by this Regulation, a certificate of authorization by such foreign company for manufacturing and marketing of the product by the applicant in Turkey. In such a case, the Ministry shall indicate in the marketing license granted to the applicant that the concerned product will be manufactured under license.

PREPARATIONS MANUFACTURED ABROAD

Article 33. Persons intending to obtain marketing authorization for a medical product manufactured abroad shall submit to the Ministry, together with the information and documents required for application pursuant to this Regulation, a certificate of authorization by such foreign company for import and sales of the product by the applicant.

CHANGE OF LICENSEE

Article 34. A third-party wishing to manufacture itself / have manufactured and market a licensed medical pharmaceutical product should request a license on its behalf, submitting the following documents to the Ministry :

1. The licence previously issued for the relevant product ,
2. A document concluded in the presence of a notary public to confirm the transfer of rights ,
3. An application file compiled by the new applicant (pursuant to Article 9).

The Ministry will evaluate this application within the framework of the relevant laws and regulations and issue a licence to the new applicant, if it deems appropriate.

OBTAINING FREE SALES AUTHORIZATION

Article 35. Prior to marketing a licensed medical product, two samples of the product ready for sale must be submitted to the Ministry and a sales authorization must be obtained. A new sales authorization permit resulting in changes in the package and label information and/or specifications of the licensed product is required.

The Ministry shall inspect the product samples with respect to insert and package information, package type, quantity per package and retail price and decide whether these are in conformity with the information and specifications taken as the basis for licensing by the Ministry.

The Ministry shall grant a sales authorization for products found appropriate.

PART FOUR

Miscellaneous and Final Provisions

PRIVACY

Article 36. Information submitted to the Ministry by the applicant to obtain a licence for a medical pharmaceutical product shall be kept confidential and the Ministry shall be responsible for the maintenance of this privacy.

INTERNATIONAL RULES

Article 37. In the selection of brand names for medical pharmaceutical products to be marketed, the rules requiring the conservation of names determined by the World Health Organization and INN (International Non-proprietary Names) should be complied with.

OTHER REGULATIONS

Article 38. Medical products for which marketing licence application is made and /or which are licensed, are subject to the provisions of the current regulations with respect to package and labeling, medical promotion, withdrawal , bioavailability, and bioequivalence.

SUPPLEMENTARY REGULATION PROCEDURES

Article 39. As authorized by Article 43 of the Government Decree in Force of Law No.181, for the purpose of protecting public health, the Ministry may add supplementary provisions to this Regulation with respect to the licensing of medical products.

CHANGE OF MANUFACTURER

Article 40. A change of the manufacturer of a licensed product is subject to the prior approval of the Ministry. The new manufacturer is obliged to conform with the conditions given in this regulation.

When applying for a change in the production site, all chemical pharmaceutical and biological data of the product and the documents related to the validation studies carried out by the new manufacturer shall be signed by the responsible manager in charge of the new production premises, and submitted to the Ministry appended to the application form.

INSPECTION ON SITE AND LIABILITY

Article 41. The Ministry will inspect on site the offices, warehouses and/or manufacturing areas, as well as the organization of personnel and distribution systems relating to the product for which the licence application is made. The company is required to submit and show the necessary documents to the Ministry officials during such inspections.

Provisional Article 1. Concerning the validity of licences for those medical products licensed prior to the effectiveness of this Regulation, applications should be made to the Ministry as described below:

1. products that have a five-year review period recorded in their licences should apply for the first renewal within this period pursuant to this Regulation; if this period is not over ,
2. products that have a five-year review period, but have already passed this period should apply at any time within 10 years after this record was made ,
3. and products that have no mention of such a period in their licences should apply within two years following the effectiveness of this Regulation.

Provisional Article 2. For medical products licensed prior to the effectiveness of this Regulation, all chemical-pharmaceutical and biological documents and Summary of Product Characteristics (SmPC) shall be prepared in accordance with this Regulation and submitted to the Ministry by the licensee within three years following effectiveness of this Regulation.

EFFECTIVENESS

Article 42. This regulation will take effect one year after its issue.

ENFORCEMENT

Article 43. The provisions of this Regulation shall be executed by the Ministry.

APPENDIX

Information and Documents to be included in Files to be submitted to the Ministry for the Registration of Medical and Pharmaceutical Products:

PART I - SUMMARY OF THE DOSSIER

A. Administrative Data

1. Pharmaceutical product
 - Name
 - Name and dose of active ingredient(s)
 - Pharmaceutical form
 - Route of administration
 - Pack size
2. Pharmacotherapeutic classification (in consideration of ATC classification of WHO).
3. Package
 - Type
 - Presentation
 - Other material for administration
4. Name, address, telephone - fax numbers of the applicant
5. Name, address, telephone - fax numbers of the person authorized to make licence applications
6. Name, address, telephone - fax numbers of the production site
7. If the product in question is to be imported:
 - a. Name, address, telephone - fax numbers of the original licence holder
 - b. Name, address, telephone - fax numbers of the manufacturer
8. Name, address, telephone - fax numbers of the place where storage and distribution will be performed
9. Countries in which the product is registered (for the first application of a product, countries where the product is registered and the approved dose, pharmaceutical form, trademarks, prescribed or OTC, restrictions applied, if any)
10. Type of application (new product, similar product, new dose, new pharmaceutical form etc.)
11. Type of the license requested (manufacturing, import etc.)
12. A list showing the number and content of the sections in the appendix submitted in support of the application (section title and page no.)
13. Name, title and signature of the applicant and date of application

B. Summary of Product Characteristics (SmPC)

1. Name of the medical product
2. Qualitative and quantitative composition (excess doses if present should be given separately)
3. Pharmaceutical form
4. Clinical information
 - 4.1. Therapeutic indication

- 4.2. Posology and method of administration
- 4.3. Contraindications
- 4.4. Special warnings and special precautions for use
- 4.5. Interaction with other medicaments and other forms of interaction
- 4.6. Use during pregnancy and lactation
- 4.7. Effect on ability to drive and use machines
- 4.8. Undesirable effects (frequency and severity)
- 4.9. Overdose (symptoms , emergency procedures , antidotes)
5. Pharmacologic particulars
 - 5.1. Pharmacodynamic particulars
 - 5.2. Pharmacokinetic particulars
 - 5.3. Pre-clinical safety data
6. Pharmaceutical particulars
 - 6.1. Quality and quantity of excipients
 - 6.2. Definition of basic manufacturing processes
 - 6.3. Finished product specifications
 - 6.4. Incompatibilities
 - 6.5. Shelf life after reconstitution and/or when the container is opened for the first time
 - 6.6. Special conditions for storage
 - 6.7. Type and nature of the container
 - 6.8. Directions for use
7. Prescription only medicine or OTC
8. Name, address, telephone - fax numbers of the registration holder
9. Date and number of the license
10. Name and address of the manufacturer (telephone, and fax no.)

C. Attachments

1. Qualitative and quantitative composition of the product (5 copies)
2. Prospectus (5 copies)
3. Package and label drafts in the original dimensions and design prepared for marketing (5 copies)
4. Authorization document with the validity date prepared by the company of origin and translation thereof (for imported / licensed products)
5. GMP certificate prepared and confirmed by the official health authority (for imported products)
6. Retail public price in the country of origin (for imported products)
7. Minimum export price (FOB) (for imported products)
8. Package and patient information leaflet samples circulated in the country of origin (for imported / licensed products)

PART II - CHEMICAL - PHARMACEUTICAL AND BIOLOGICAL DATA

A. Composition

1. Composition of the preparation
 - a. Name, quantity, function in the formula and reference of the active ingredient (s)
 - b. Name, quantity, function in the formula and reference of the excipient(s)
2. Container description
 - a. Nature of the container material
 - b. Qualitative composition

- c. Closure system
- d. Opening method
- 3. Pharmaceutical development of the preparation
 - a. Choice of the formulation
 - b. Choice of the materials in the composition
 - c. Choice of the container
 - d. Effects of the materials in the composition on stability and other characteristics
- 4. Clinical research formula (if necessary)

B. Manufacturing Method

- 1. Manufacturing formula (including details of batch size)
- 2. Manufacturing process (all processes beginning from the starting materials)
- 3. Manufacture flow scheme
- 4. In-process controls

C. Control of Starting Materials

- 1. Active ingredients
 - 1.1. Specifications and routine tests
 - 1.1.1. Active ingredients described in pharmacopoeias
 - 1.1.2. Active ingredients not described in pharmacopoeias
 - Characteristics
 - Identification tests (detection)
 - Purity tests (including acceptability limits of identified one and total impurities)
 - Physical purity
 - Chemical purity
 - Biological / immunological purity* (for biological / biotechnological active ingredients)
 - Potential contamination by microorganisms, products of microorganism, pesticides, toxic metals , radioactivity , fumigants , etc. * *
 - Other tests
 - Assay(s) and/or other evaluation of potency*
 - Assay(s) of constituents of herbal drugs or herbal drug preparations with known therapeutic activity**
 - A monograph of the herbal drug in herbal drug preparations* *
- 1.2. Scientific data
 - 1.2.1. Nomenclature
 - INN name
 - Chemical name
 - Other names
 - Laboratory code
 - For herbal preparations**
 - Scientific name of plant, species, type, variety and chemotype of the herb
 - Parts of the herb used
 - Name of the preparation
 - 1.2.2. Description
 - Physical form
 - Structural formula (macro molecular conformational data)
 - Molecular formula

- Relative molecular weight
- Chirality
- Recent scientific data on the basic materials of herbal drugs**

1.2.3. Manufacture

- Name and address of the manufacturing source*
- Geographical source of the herbal drug* *
- Synthesis or the way of obtaining the product
- Culture, media, and other additives*
- Description of the manufacturing process***
- Solvents, reactives, and other ingredients**
- Catalysts* * *
- Purification procedures***

1.2.4. Quality Control During Manufacturing Process***

- Starting Materials
- Intermediate product control (if necessary)
- Seed lots* (master and working)
- Ingredients of the culture medium and other additives*
- Specifications for the material used in purification procedure*

1.2.5. (A) Development Chemistry for Chemical Active Ingredients* * *

- Proof of the chemical structure (synthesis method , basic intermediate products , elemental analysis , Mass spectrum, NMR, IR, UV, and others)
- Potential isomerism
- Physico-chemical characteristics (solubility, physical characteristics, polymorphism, pKa, and pH values , and others)
- All specifications of the primary reference material
- Analytical validation and comments on the selection of routine tests and standards (e.g.working standard)

(B) Development for Biological / Biotechnological Active Ingredients*

- Expression vector, host cell, entry of the vector into the host cell, and condition thereof
- Sequence determination and stability of the cloned gene
- Expression strategy
- Master (main) seed bank
- Stability of the host cell / vector characteristics (including end of manufacturing process)
- Modifications after conversion
- Proof of the structure of the active ingredient
- Biological and physico-chemical criteria
- Selection of norms and routine experiments, validation thereof and analytical development

(C) Development for herbal active ingredients**

1. Herbal drug

- Description of the herbal drug
 - Macroscopic
 - Microscopic
- Composition, physical properties and analytical examination of ingredients
- Examination of adulterants with known toxic ingredients
- Analytical development and validation, comments on the choice of routine tests and specifications

2. Herbal drug preparations (e.g. powder, extract)

- Chemical analytical profile (qualitative and quantitative)
- Determining the toxic ingredients /adulterant materials
- Analytical development and validation, comments on the choice of routine tests

and specifications

1.2.6. Impurities

- Potential impurities originating from the route of synthesis
- Impurities determined and structural deviations found
- Impurities arising from vector-host cell system
- Impurities arising during manufacturing and purification
- Impurities formed during transcription, translation or post-translational conversion and showing structural change*

- Methods of detecting potential contamination of herbal drug by microorganisms or their products, pesticides, fumigants, toxic metals, radioactivity etc. thereof * *

- Potential adulterants of herbal drugs

1.2.7. Batch analysis

- Batches tested (manufacturing date, manufacturing place, batch size, batches used in clinical studies)

- Test results
- Reference material (analytical results)

2. Other Ingredients

2.1. Specifications and routine tests

2.1.1. Ingredients described in pharmacopoeia

2.1.2. Ingredients not described in pharmacopoeia

- Characteristics
- Identification tests
- Purity tests (limits of identified single and total impurity and those of unidentified single and total impurities)
 - Physical purity
 - Chemical purity
 - Biological / immunological purity*
- Other tests
- Assay(s) and/or evaluation (where necessary)

2.2. Scientific data

For an excipient to be added in the composition of preparations for the first time (as in active ingredients section)

3. Packaging Material (Primary package)

3.1. Specifications and routine tests

- Type of the material
- Structure of the material
- Quality specifications, routine tests, and test methods

3.2. Scientific data* * *

- Development studies on package material
- Batch analysis, analytical results

D. Control Tests on the Intermediate Products (if necessary)

A distinction should be made between in-process controls and control tests on intermediate products.

E. Control Tests on the Finished Product

1. Specifications and routine tests

1.1. Product specifications and test for release (at the time of manufacture)

1.2. Control methods

1.2.1. For active ingredients

- Identification tests
- Assay(s) (when necessary biological and microbiological methods), for herbal drugs and preparations quantitative determination of constituents with known therapeutic activity

- Purity tests

1.2.2. Pharmaceutical tests (e.g. dissolution)

1.2.3. Microbiological controls - pyrogen control (when necessary)

1.2.4. Identification and determination of excipients

- Identification of coloring materials

- Determination of antimicrobial or chemical preservatives (with limits)

2. Scientific data

2.1. Comments on the choice of routine tests used for finished product controls and standards

2.2. Batch analysis

- Batches tested (manufacturing date, place of manufacturing, batch size etc.)

- Results obtained

- Reference materials, primary and others

F. Stability

1. Stability tests on active ingredients

- Batches tested

- General test methodology

- Accelerated test conditions

- Normal test conditions

- Analytical test methods

- Assay

- Determination of degradation products

- Validation of test methods including limits of detection

- Test results

- Comments and conclusion

2. Stability tests on the finished products

- Quality characteristics for the recommended shelf life

- Number of the batch tested - packagings

- Study methods

- Real period studies

- Studies under other conditions (accelerated)

- Characteristics investigated

- Physical characteristics
- Microbiology
- Chemical
- Chromatographic
- Characteristics of package (product interaction with closure /container

system)

- Evaluation of test procedures
 - Description of the test methods
 - Validation of test methods
- Test results (including initial values and degradation products)
- Results
 - Shelf-life and storage conditions
 - Shelf-life after reconstitution and/or first opening of the product
 - Ongoing stability studies

PART III - TOXICOLOGICAL AND PHARMACOLOGICAL INFORMATION

The following information must be provided in respect of each test:

1. Animals used (species, sex, age, weight , etc.)
 2. Product used (series no., quality, etc.)
 3. Experiment conditions (diet , husbandry , etc.)
 4. Results
- A. Single dose toxicity
 - B. Repeated dose toxicity
 1. Subacute toxicity experiments (up to three months)
 2. Chronic toxicity experiments (after three months)
 - C. Studies on Reproduction
 1. Effect on fertility and general reproductive performances
 2. Embryo-toxicity
 3. Perinatal / postnatal toxicity
 - D. Mutagenic potential
 1. In-vitro
 2. In-vivo
 - E. Oncogenic / carcinogenic potential
 - F. Pharmacodynamic data
 1. Pharmacodynamic effects relating to proposed indications
 2. General pharmacodynamics
 3. Drug interactions
 - G. Pharmacokinetic data
 1. Pharmacokinetics after single dose
 2. Pharmacokinetics after repeated administration
 3. Distribution in normal and pregnant animals (e.g. autoradiography)
 4. Biotransformation
 - H. Local tolerance (toxicity) (where appropriate)
 - Q. Other information
- This section is intended for possible information not covered by any of the previous sections.

PART IV - CLINICAL DOCUMENTATION

- A. Clinical Pharmacology
 1. Pharmacodynamics

The information below must be supplied in connection with each study:

1.1. A summary

1.2. A detailed research plan (protocol)

1.3. Findings including the following:

- characteristics of the population studied
- findings with respect to efficacy
- clinical and biological findings with respect to safety (charts demonstrating that such findings are beneficial)
- analysis of the findings

1.4. Results

1.5. Bibliography (if any)

2. Pharmacokinetics

Findings of the research must be given in terms of the groups studied:

- Healthy volunteers
- Patients
- Special patient groups / special pathological conditions (elderly people, renal or hepatic insufficiency, etc.)

The following must be submitted for each study:

2.1. A summary

2.2. A detailed research plan (protocol)

2.3. Findings

2.4. Results

2.5. Bibliography (if necessary)

B. Clinical Evaluation

1. Clinical trials

The following must be submitted for each clinical trial:

1.1. A summary

1.2. A detailed description of main points and analytical methods in the research plan (protocol) (or the protocol itself)

1.3. Final (or interim) report including the following:

- Characteristics of the groups studied
- Findings with respect to efficacy
 - Clinical and biological observation
 - Main criterion of efficacy
 - Other criteria
- Clinical and biological findings with respect to safety
- Statistical evaluation of the findings
- Data regarding each patient
 - Charted data regarding patients including clinical and laboratory observations

1.4. Discussion

1.5. Result

2. Post-marketing experience

2.1. Adverse reactions and the related monitored events and reports

2.2. Number of patients exposed to post-marketing application

3. Published and unpublished clinical trials (other than 1)
 - 3.1. Brief information on ongoing and uncompleted trials
 - 3.2. Any other information

P.S. : (*) These are necessary only for biological or biotechnological products
(* *) These are necessary only for products derived from plants
(***) These are submitted on request in the case of brief applications