

Instruction on drug registration, manufacture & Imports

On the basis of the law related to regulations on medical and pharmaceutical and food & beverages affairs, ratified in 1955 and its further amendments and the rules and regulation of registration, Manufacturing & imports approved on Apr.8.2009 by the Minister of Health & Medical Education (No. D/1243 dated Apr.9.2009), the instruction for drug registration is notified as follow:

1. DEFINITIONS

- 1.1. **Generic drug** should mean a drug containing the same active ingredients as the innovator brand and interchangeable, supplied to the market by one or several independent manufacturers. A generic drug manufactured under information nonproprietary name which is called INN-generic, and that manufactured under proprietary name, branded-generic.
- 1.2. **An original or innovator brand** is a drug obtained as the result of a person's or company's innovation and registered in the name of the inventor with its formula, name and proprietary mark in Iran or other countries.
- 1.3. **A biological product** should mean a product with human, animal, microbial and cellular origin required to be controlled and supervised different from those on usual drugs because of its molecular specified characteristics.
- 1.4. **A biosimilar** is a biologic product containing the same active ingredients as the biologic innovator brand and interchangeable. Comparative clinic studies are required to prove the equal curing effect of such drugs because of the large size and complexity of their molecules.
- 1.5. **DPNA** should mean the division of pharmaceutical & narcotic affairs in the food and drug deputy of ministry of health and medical education which is responsible for regulation of medicines.
- 1.6. **A license** is an official certificate issued by DPNA in the name of a specific legal entity in accordance with the regulations for a pharmaceuticals product after registrations and approval of safety, effectiveness, quality, efficacy and pricing.
- 1.7. **Marketing Authorization Holder (MAH) or License Holder (LH)** is a registered company in IRAN having qualification and permits required for registering and promoting its drugs. Such company should be liable for all issues such as safety, quality, price and promoting of the drugs in IRAN's market.
- 1.8. **A manufacturer** is a legal entity having hardware (site, buildings, machinery and technical equipments) and software (man power, technical knowledge, SOPs and documentation systems) qualification in accordance with current good manufacturing practice (cGMP) and obtained such permits as required by DPNA.
- 1.9. **An importer** is a company having qualification in accordance with good distributing practice (GDP) and good storage practice (GSP) obtained such permits as required by DPNA.
- 1.10. **The Council of Experts** is the commission as provided in paragraph 2, article 20 of the law related to regulations on medical, pharmaceutical and food & beverages affairs, ratified in 1955 and its further amendments which is authorized for establishing all registration, import and manufacturing permits and licenses, also for authorizing responsible pharmacists in the companies. Deputy Minister for Food & Drug, Director General of DPNA, Director General of Laboratories of MOH, three selected board members of universities of medical sciences (two pharmacists, one physician), a representative of pharmaceutical companies (head of syndicate) and the general manager of the odd governmental import company are the members of the commission.
- 1.11. **Responsible pharmacist** is a person who has obtained a qualified license from the council of experts. Responsible pharmacist is liable for complying with regulations and standards provided by DPNA in each company and its duties are defined in accordance with the subject matter of the relevant company. Usually QA manager could name as responsible pharmacist after the council of experts approval.
- 1.12. **The pricing commission** means such commission as provided in note 3, paragraph 4 article 20, of the law related to regulations on medical and pharmaceutical and food and beverages affairs ratified in 1955 and its further amendments authorized for pricing all pharmaceuticals. Deputy Minister for Food & Drug, Director General of DPNA, a representative of pharmaceutical companies (head of syndicate), a representative of the ministry of commerce and the general manager of the odd governmental importing company are the members of the commission.

2. THE COMPANY ESTABLISHMENT

2.1. **Market Authorizing Holder or License Holder.** Activity license for the relevant company will be issued in two steps:

2.1.1. First step: Agreement in principle will be issued after the submission of the following documents upon the approval of the council of experts. Such agreement will be valid six months and the company is required to proceed with obtaining the activity license after completing the relevant requirement. Agreement in principle may be extended only two times upon the presentation of the adequate justification:

- filled application form for company's specifications (enclosed)
- Articles of association and notice of incorporation of the company in the official gazette with the subject matter of pharmaceutical activity.
- No effective penalty records.

2.1.2. Second step: activity license for the company will be issued upon the presentation of the following documents. After such step the company may proceed with registering the drug such activity license will be valid for 4 years:

- Documents supporting good quality assurance and market vigilance practice of the company. Details of the facilities in this respect depend on the number and properties of the registered drugs.
- Establishing a control laboratory or entering into agreement with a control laboratory.
- Approval issued by the technical expertise inspector.
- appointment of a responsible pharmacist meeting the following requirements:
 - Having a doctorate degree in pharmacy.
 - Having a pharmacist license for Islamic republic of Iran.
 - No effective penalty records.
 - Qualifications approved by the Ministry of Health.
 - Minimum one year of experience in the relevant pharmaceutical establishments.

2.2. **Manufacturers,** license holders or marketing authorization holders are required to manufacture their registered medicines in facilities inside or outside the country holding a current good manufacturing practice (cGMP) issued by DPNA. Obtaining such certificate before proceeding with registering issue for pharmaceutical products is mandatory. Regardless of companies manufacturing abroad, they should present the same certificate issued by the organization in charge of pharmaceutical industries in the country of origin. To obtain such certificate domestic pharmaceutical plants should first obtain their establishment license and Appointment of a responsible pharmacist. Certificate of current good manufacturing practice regards the continuity of current good manufacturing of drugs. The certificate is valid for 2 years and will be evaluated in periodical inspections by DPNA inspectors.

2.3. **Importers,** import companies are authorized to proceed with commercial issues and imports of pharmaceuticals relevant to marketing authorization holders or license holders after having obtained the required authorizations. These companies are authorized to import those drugs for which a drug marketing authorization or license has been issued earlier. To obtain an import license having the following requirements is a must:

- Article of associations of the company with subject matter of imports of drugs.
- Last official gazette.
- No effective penalty records.
- Record of pharmaceutical establishments.
- Qualification approved by the council of experts.
- Documents supporting good storage and distribution practice of the company.

License holders may directly perform its commercial activities or assign it to import companies. Meanwhile, such assignment of commercial activities should not relieve the license holder from its liabilities.

In specific and emergency cases, non-registered or under registration medicines may be imported at the discretion of DPNA after approval of the council of experts. In such cases the import company should be liable for quality control and assurance of the imported product.

3. DRUG REGISTRATION LICENSE

3.1. Drug registration should be carried out in two steps. During the first step, the registering company should apply for the registration of the product by submitting the following documents:

- 3.1.1. Application for product registration (enclosed).
- 3.1.2. cGMP certificate issued by the competent authority of the country of manufacturing (no GMP visit in this part) or technical approval by DPNA, stating the possibility of manufacturing such product at the defined facility.
- 3.1.3. Valid agreement executed between the license holder in Iran and the main company holding the main license or the manufacturer recognizing the Iranian registering company as the license holder/Market Authorizing Holder of the drug in Iran and assigning all responsibilities.

Basing on the information and specifications provided in the application for drug registration, DPNA will notify the applicant of its decision within 45 days as of the date of application after having carried out the required expertise and discussed the matter in council of experts. In this event that the active ingredients molecule of the drug in question as to its application is not earlier registered in the country the matter will be referred to the Drug Selection Board and no more subject to 45 day time planning.

In the letter of agreement in principle for drug registration, the following matters will be notified to the company:

- Terms approved by the council of experts.
- Specific standards, related to controlled products.
- Obligation of performing clinical studies.
- Price or price terms approved by drug pricing commission.
- Time required for assessment of the file which is supposed to be complete without any deficiency.
- Approximate date of GMP inspections, if required.
- Date of commencement of assessment of the file regarding the number of files in the line of registration and priorities of DPNA. The assessment of the files commences on the basis of first in first out (FIFO). There is a fast tract during which the files are assessed immediately after the issue of the initial agreement and completion of the documents by the applicant includes the following:
 - Those drugs of which the active ingredients have no previous equivalent regarding their first 4 characters of ATC.
 - Those drugs of which the active ingredients in the same dosage form has never been registered in the country.
 - A drug selected by the company against every million dollar exports (for domestic manufacturers)
 - A drug selected by the company against every certificate of GMP obtained (for domestic manufacturers).
 - Originator brand manufactured in the country.
 - List of document and supporting papers required for drug registration.

Registration with proprietary name should meet the following requirements:

- Having at least 3 characters different from other names registered in the country.
- Avoid any unusual reference.
- Avoid using Greek characters (α , β ...) or figures.
- Avoid from any similarity with the name of different pharmaceutical and treatment groups.
- Avoid from any similarities with logo or name of other companies.
- Non-proprietary name of drug may not be partially used as a proprietary name.
- Avoid from including prefixes and suffixes advocating specific significations, formulas, strengths, indications of use, or abbreviations commonly used in pharmaceutical activities.

3.2. During the second step, the applicant should submit the require documents at the due date in the letter of agreement in principle. List of documents are as following (if any specific documents required, the applicant will be notified thereof in the letter of agreement in principle):

- Dossier according to electronic common technical document (eCTD).
- cGMP certificate of manufacturing company (site inspection may be carried out before or during the assessment of the file).

- Free Sale Certificate (or Certificate of Pharmaceutical Products) of Ministry of Health of the country of origin for those drugs whose original license holder is not Iranian.
- Undertaking of supply at the approved price.
- Registration fee payment slips according to the approvals of the annual budget.

After technical assessment and expertise, DPNA will notify the applicant of deficiencies, missing documents, and necessary recommendations. The applicant should then send full response in one time and complete the dossier within the fixed time limit. DPNA will issue the license after remedying deficiencies and completion of documents and approval of the dossier. Time for assessment of the dossier is calculated on a clock off basis not exceeding 180 days. If the examination exceed such time or any technical disagreement occurs for the approval of the dossier, the council of experts will take in charge the case and deliver it thereon. License includes full specifications of the drugs, license holder, drug national code, manufacturing facility, responsible pharmacist, formula, date of approval by the commissions, consumer price, validity, license holder's undertakings and terms of distribution and supply. Such license will be valid 4 years, in specific cases, the council of experts may issue license with validities less than 4 years.

- 3.3. As regards the renewal of license, the matter will be examined after the submittal of the following documents. Upon the approval the council of experts, a new license will be issued prior to the expiry date of the said license:
 - renewal application submitted 6 months prior to the expiry date of the license together with the list of all changes carried out in formulation, packaging specifications and source of raw materials including active ingredients and packaging materials.
 - Submittal of new full dossier in case of changes affecting the pharmacokinetics of the product.
 - List of general specification of released batch along with a report on the amount of each batch sold in the country.
 - general specification of defected batches and those entailing claims, side effects or recall, taken in charge by post marketing surveillance division of the company together with the measures for dealing therewith (PSURs).
 - Result of any ongoing studies in the country (clinical or non-clinical) on the product.
 - Application for changing the price, if required (during the validity of each license, prices may be changed two times).
 - Previous License.
 - Registration fee payment slips for renewal in compliance with the budget act.
- 3.4. non-compliance with any terms of the marketing authorization or any breach of the terms specified therein as well as any change in drug procurement and supply violating the standards notified by DPNA will result in cancellation or provisional suspension of the license upon the approval of **The Council of Experts**.
- 3.5. The exclusivity of new entities manufactured for the first time in the country could be provided upon the approval of the commission.
- 3.6. Performing clinical studies in the country in accordance with good clinical practice should be required in the following cases. In such cases, prior to the commencement of clinical studies proposal **should be** approved by a credible research center or pharmaceuticals faculties of the country and the relevant ethic committee:
 - New entities whose active ingredients have never been used in humans.
 - Registered drugs which are claimed to be intended for a new indication.
 - Biosimilars. The council of experts may except or simplify this part for domestically produced biosimilars obtaining approval of reference laboratories regarding bioequivalence to the innovator brand. In these cases the clinical studies are continued and the license will be issued after completion of clinical studies.
- 3.7. Specifications of every batch of the registered drug should be controlled by responsible pharmacist of license holder before supply to the market in order to obtain a lot/batch release. A copy of batch/lot release should be submitted to DPNA (on paper or electronically) . Lot or batch release of every batch of vaccines and blood products is carried out DPNA Therefore, as regards such cases, release documents should be sent.

- 3.8. Registration, manufacturing and imports of narcotic and controlled drugs as well as their intermediates should be subject to specific regulations and standards governing thereon in addition to drugs general regulations.
- 3.9. All medicines should be priced at the discretion of pricing commission. The price will be fixed and declared in Iranian Rial and in three levels of license holder, distributor and pharmacy. In drug pricing, the above commission should take the following factors into consideration:
- Price of the innovative brand and other generics in reference countries fixed by pricing commission (Spain, Greece, Turkey, and manufacturing country).
 - Raw materials and production costs.
 - Consumer's purchasing power.
 - Formulation and special characteristics of the drug and manufacturing conditions.
- Distributor's margin depending on the price, weight, volume and distribution conditions will be separately calculated for each drug and declared upon the approval of the pricing commission. Drug consumer price may be revised once a year at maximum and twice during the validity of each license upon submittal of documents and supporting proof documents. Commercial duties should all be applied to imported drugs whose generic type domestically manufactured covers at least 50% of the market during 6 continuous months.
- 3.10. Promotion, marketing, and advertisement of drugs in any manner is authorized at the license holder's responsibility and in compliance with the provisions of by-laws provided in notes 5 to article 14 of law on medical & pharmaceutical affairs regulations.