

## **ANMAT Order No 5260/2008**

HAVING REGARD TO Laws Nos 16.463, 17.818, 19.303; Decrees Nos 9763/64, 150/92, 1890/92, 177/93; Joint Resolutions Nos 268/92 (M.S. and A.S.) and 470/92 (M.E. and O.S.P.) and No 748/92 (M.S. and A.S.) and 988/92 (M.E. and O.S.P.), Decree No 1490/92, Common Market Group (*Grupo Mercado Común*, GMC) Resolution No 88/93, transposed into national law through ANMAT Order No 5219/97, Order (ANMAT) No 2819/04, the reports from the PICs (Pharmaceutical Inspection Cooperation Scheme) and dossier 1-47-1110-419-08-1 from the Register of this National Authority, and

### **WHEREAS:**

The active ingredients intended for use in the manufacture of medicines are included in the scope of Articles 1, 2 and 3 of Law No 16.463;

Article 1 b) of Decree No 150/92 defines an active ingredient or pharmaceutical drug as “any chemical or mixture of related substances of natural or synthetic origin which, having specific pharmacological properties, is used in human medicine”.

Chapter III (Articles 7, 8 and 9) of the Decree referred to in the previous recital lays down the requirements to be met by establishments that manufacture and/or portion drugs and medicines.

In accordance with Decree No 1490/92, which instituted it, the National Medicines, Foods and Medical Technology Board (ANMAT) is responsible for all matters relating to the monitoring and inspection of the healthfulness and quality of drugs, chemicals, reagents, pharmaceutical forms, medicines, elements of diagnosis, biomedical materials and technology and all other products used and applied in human medicine and to the control of the activities, processes and technologies used in the supply, production, manufacture, portioning, import and/or export, storage and sale of products, substances, elements and materials consumed or used in human medicine (Article 3(a) and (e)).

In keeping with the above responsibility Decree No 1490/92 gives ANMAT powers to authorise and register the said products, oversee compliance with the health and quality rules laid down for them and grant authorisation to the natural or legal persons involved in the supply, production, manufacture, portioning, import and/or export, storage and sale of the same.

Such activities are primarily intended to guarantee the effectiveness, safety and quality of the products consumed by the public.

In order to perform these supervisory activities, provided for in Article 8(n) of Decree 1490/92, it is necessary to have a model that ensures that industries are supervised using harmonised criteria as well as neutrality, symmetry and reciprocity in the treatment and application of the regulatory standards on the production of medicines from the raw material to the finished product.

It was with this in mind that ANMAT Order No 2819/04 was enacted, adopting the recommendations in force concerning Good Manufacturing and Supervisory Practices for 2003, approved by the World Health Organisation, and reports by the Pharmaceutical Inspection Cooperation Schemes: PE 009-1 and ICH —International Conference on Harmonisation — Guide Q7A on Good Manufacturing Practice for active pharmaceutical ingredients (API) included as Annex VI, compliance with which – or with any rules that may replace it in future – is compulsory for establishments engaged in the manufacture, preparation, portioning, import and/or export of active pharmaceutical ingredients (API).

In accordance with its duty of verifying compliance with Good Manufacturing Practice, this Authority draws attention to the need to update the legislation in force and considers it appropriate to make use of the powers conferred by Article 8 (ñ) of Decree 1490/92 and Decree 341/92, which authorise it to adopt the most timely and appropriate measures to protect the health of the population.

Article 6(2) of Joint Resolution No 268/92 (M.S. and A.S.) and No 470/92 (M.E. and O.S.P.) amended by the similar instrument No 748/92 (M.S. and A.S.) and N° 988/92 (M.E. and O.S.P.) specifies the professional qualifications required for access to technical management positions as regards activities relating to pharmaceutical drugs or active ingredients in medicines.

Since our country is a signatory of the United Nations Single Convention on Narcotic Drugs of 1961, its amended Protocol of 1971 and the Convention on Psychotropic Substances of 1972, it must submit to the International Narcotics Control Board (INCB), before July 31 each year, its forecasts for imports and local manufacture of narcotics and psychotropic substances for the following year.

It is necessary to lay down rules that increase the predictability of the system under which companies engaged in activities of manufacture, preparation, portioning, import and/or export of active pharmaceutical ingredients (API) are registered.

Common Market Group Resolution No 88/93 adopted the Technical Document known as “Authorising the operation of pharmaceutical chemical plants”, and this was transposed into national law by ANMAT Order No 5219/97.

In accordance with the previous recital, it has become necessary within the framework of MERCOSUR to implement a first phase in relation to compliance with the rules laid down in the Document “Authorising the operation of pharmaceutical chemical plants”, by means of the authorisation of the plants in the sector by the Health Authority.

The authorisation of establishments that manufacture/prepare, package, import and/or export medicines includes requirements that apply equally to those engaged in the manufacture, preparation, portioning, import and/or export of active pharmaceutical ingredients (API).

The National Medicines Institute and the Legal Affairs Directorate have taken the appropriate action.

This action was taken under the terms of Decree No 1490/92 and Decree No 253/02,

Therefore,

THE INSPECTOR OF THE NATIONAL MEDICINES, FOODS AND MEDICAL TECHNOLOGY

BOARD

DECREES:

**Article I** — This Order shall apply to the activities of manufacture/preparation, distribution, import, export and/or storage under the national jurisdiction or for the purposes of inter-jurisdictional trade of active pharmaceutical ingredients of chemical synthesis and the natural or legal persons involved in such activities.

**Article 2** — The activities referred to in the previous article may only take place with the authorisation and under the control of this National Authority, in establishments authorised for the same, which must comply with all of the requirements laid down in this Order and with the Good Manufacturing Practices included in Annex VI to ANMAT Order No 2819/04 or those that may replace them in future.

**Article 3** — For the purposes of this Order the following definitions are hereby adopted:

- a) **CONTRACTED PRODUCER:** Establishment authorised by ANMAT that performs some of the stages in the manufacturing process as agreed with the licensed undertaking under a contract.
- b) **UNDERTAKING LICENSED TO PRODUCE, PORTION, IMPORT AND/OR EXPORT:** natural or legal person authorised by ANMAT to manufacture, produce, portion, import and/or export active pharmaceutical ingredients (API). This party is responsible for the release of the batches in accordance with the quality targets required under this Order.
- c) **MANUFACTURE/PRODUCTION:** Total synthesis of an active pharmaceutical ingredient (API) or partial synthesis from a specific element, which may include the following operations: receipt of materials, production, packaging, repackaging, labelling, relabelling, quality control, dispatch, storage and distribution.
- d) **PORTIONING:** all operations of receipt of an active pharmaceutical ingredient, division into smaller packages or units, packaging, labelling, quality control, dispatch, storage and the associated controls.
- e) **ACTIVE PHARMACEUTICAL INGREDIENT (API):** Any substance or mixture of substances intended for use in the manufacture of a medicine or medicinal preparation and that thus becomes an active ingredient in the said product, including those classified as psychotropic under Law No 19.303 and its annexed lists or as narcotics under Law No 17.818 and its annexed lists.

These substances have pharmacological properties or other direct effects on the diagnosis, cure, relief, treatment or prevention of illnesses, or influence the structure and function of the human body.

f) **INTERMEDIARY:** a material prepared during the stages of processing of an active pharmaceutical ingredient that undergoes additional molecular changes before being transformed into an active pharmaceutical ingredient. Intermediaries may or may not be isolated.

g) **BATCH:** specific quantity of material produced during a process or series of processes that is homogeneous within the specified limits.

In the case of continuous production a batch may correspond to a defined proportion of the production. The size of the batch can be defined either as a fixed quantity or as the amount produced over a given period of time.

h) **PACKAGING AND PACKING MATERIAL:** elements intended to protect an active pharmaceutical ingredient during packaging, storage or transport.

i) **BATCH NUMBER:** unique combination of numbers, letters and/or symbols identifying a batch and which can be used to determine the history of the production and distribution.

**Article 4** — The undertakings referred to in Article 2 of this Order must have a pharmaceutical professional as the technical manager of the undertaking, and sufficient staff with the appropriate training, so that the quality of the active pharmaceutical ingredients (API) and the performance of the quality controls required under this Order can be ensured at all times.

**Article 5** — The undertakings referred to in Article 2 of this Order must have a minimum infrastructure made up of one production and portioning area, storage area and a properly-equipped in-house quality control laboratory, in accordance with the activity for which the undertaking is authorised, and may contract out to a third party the quality controls referred to in Article 13 of this Order.

**Article 6** — The active pharmaceutical ingredients prepared and/or imported must meet the technical quality specifications laid down in the current *Farmacopea Argentina* (FA), the British Pharmacopoeia (BP), the European Pharmacopoeia (EP), the *Farmacopeia Brasileira* (FB), the *Farmacopea de los Estados Unidos Mexicanos* (FEUM), the International Pharmacopoeia (WHO), the Japanese Pharmacopoeia (JP) and the United States Pharmacopoeia National Formulary (USP-NF), and/or, failing this, they must comply with the manufacturer's specifications.

**Article 7** — The undertakings mentioned in Article 2 of this Order and which are currently operating must comply with the provisions laid down herein within a period of ninety (90) days following its publication in the Official Gazette by applying for the corresponding authorisation. To this end they must submit to ANMAT the required information shown in Annex I, which is an integral part of this Order.

**Article 8** — Undertakings with authorisation to manufacture medicinal preparations shall be automatically authorised to perform activities of portioning, import and/or storage of active pharmaceutical ingredients for their own use, and must comply with the technical requirements laid down in this Order.

To monitor compliance with the provisions of the previous paragraph ANMAT, through the National Medicines Institute (INAME), will perform the inspections it considers necessary in order to determine the exactitude of the information declared.

**Article 9** — Changes to the physical structure of the authorised establishments and facilities must be authorised by this National Authority, which will check them beforehand by means of an inspection.

**Article 10.** — An undertaking authorised to produce active pharmaceutical ingredients (API) may delegate the performance of any of the stages in the manufacturing process to other producing undertakings, authorised by ANMAT, which will be known as “Contracted Producers”.

The legal relationship between the licensed undertaking and the contracted producer must take the form of a written contract setting out the stages in the production process for which each of the parties is responsible and must be signed by the Technical Managers and legal representatives of both undertakings.

**Article 11.** — The licensed undertaking that contracts out production must keep up-to-date records of the work contracted out, indicating the batches manufactured and released in order to document and guarantee the traceability of the same.

**Article 12.** — The licensed undertaking and the contracted undertaking(s) shall be jointly and severally responsible for the activities of manufacture, preparation, portioning, import and export of active

pharmaceutical ingredients, as well as for compliance with the Good Manufacturing Practices.

**Article 13.** — The authorised undertakings may contract out to third parties those quality controls that require special facilities, equipment and/or procedures.

The contract between the licensed undertaking and the contractor must be made in writing and shall set out all of the checks involved for which each party is responsible. This must be signed by the Technical Managers of the parties involved and their legal representatives.

The contracted laboratory shall also be subject to inspections by this National Authority.

**Article 14.** — Undertakings authorised to produce active pharmaceutical ingredients may obtain certification for the products produced and sold following evaluation by this National Authority of the documentation required in Annex II, which is an integral part of this Order. These active pharmaceutical ingredients shall form part of the update to the *Farmacopea Argentina* and the National Programme of Development of Reference Substances.

**Article 15.** — To be registered and recorded. To be communicated to the Chambers and other Professional Bodies. To be notified to the relevant parties. To be given to the National Directorate for the Official Register for publication. Once completed, to be permanently archived. — Ricardo Martínez.

## ANNEX I

### APPLICATION FOR AUTHORISATION OF UNDERTAKING

Messrs ..... and ....., in our capacity of owner/legal representative and technical manager, respectively, of the undertaking ..... are writing to you to request inspection of our establishment to verify compliance with the Good Manufacturing Practices of active pharmaceutical ingredients (API), and declare the information provided below to be exact:

#### 1. IDENTIFICATION OF THE UNDERTAKING

- Name/Business name:
- Legal representative (attach documents demonstrating legal status):
- Tax number:
- Registered address of the head offices of the undertaking (plants, storage facilities, etc.):
- Telephone and fax:
- E-mail:

#### 2. THIRD-PARTY CONTRACTORS:

- Name/Business name:
- Legal representative (attach documents demonstrating legal status):
- Tax number:
- Registered address of the head offices of the undertaking (plants, storage facilities, etc.):
- Telephone and fax:
- E-mail:

#### 3. ACTIVITIES PERFORMED BY THE UNDERTAKING:

- Preparation: YES/NO
- Portioning: YES/NO
- Import: YES/NO
- Export: YES/NO

#### 4 PRODUCTS INVOLVED IN THE MANUFACTURING, PRODUCTION, PORTIONING, IMPORT, EXPORT AND/OR SALES-RELATED ACTIVITIES PERFORMED BY THE UNDERTAKING

#### 5 IDENTIFICATION OF THE TECHNICAL MANAGER:

- Name and surname:
- National identity card number:
- Registration number:
- Attach a certified photocopy of the qualification and registration

6. PHYSICAL STRUCTURE:

- Attach original and two copies of most up-to-date plans, at scale 1:100:

7. PRODUCTION AND CONTROL EQUIPMENT

- List of items of equipment used:

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**SIGNATURE**

**OWNER/LEGAL REPRESENTATIVE**

**SIGNATURE**

**TECHNICAL MANAGER**

ANNEX II

CERTIFICATION OF ACTIVE PHARMACEUTICAL INGREDIENTS MANUFACTURED IN THE  
COUNTRY

1.- DETAILS OF THE PRODUCT:

Product name:

ATC pharmacological classification:

2. - DETAILS OF THE APPLICANT LICENSED UNDERTAKING:

Name or business name:

Registered address:

Registered address of the manufacturing plant:

Telephone and fax:

E-mail

Website:

Tax number:

Number of authorising order:

3 DETAILS OF THE TECHNICAL MANAGER:

Name and surname:

Type and number of document:

Order authorising the technical manager:

4 DETAILS OF THE LEGAL REPRESENTATIVE:

Name and surname:

Address:

Telephone and fax:

Type and number of document:

5 – CONTRACTED MANUFACTURING UNDERTAKING, IF ANY:

Name or business name:

Registered address:

Registered address of the manufacturing plant:

Telephone and fax:

E-mail:

Website:

Number of Order authorising the undertaking:

Name of technical manager of manufacturing undertaking:

Number of Order registering the technical manager:

Contract:

#### 6. - QUALITY CONTROL BY THIRD PARTIES

Name or business name of contracted laboratory:

Address:

Telephone and fax:

Name of technical manager of contracted laboratory:

Copy of the contract:

#### 7. -REQUIRED TECHNICAL DOCUMENTATION:

##### MANUFACTURE

- Description of manufacturing process and process controls

- Flowchart

- Critical Control Points

- Validation or evaluation of the manufacturing process

- For sterile drugs: validation of sterilisation process

- Development of the manufacturing process

- Expected yield

##### • GENERAL INFORMATION AND CHARACTERISATION

- Nomenclature

- Structure: Molecular weight, molecular and structural formula

- Properties: General characteristics, solubility, crystalline form, chirality, particle size

- Elucidation of structure and other characteristics

##### • CHECKS ON INTERMEDIARIES AND STARTING MATERIALS

- Sampling techniques

- General features

- Analytical methods

v Physical tests

v Identification tests

v Tests of purity

v Evaluation methods

- Specifications
- Justification of specifications
- Elucidation of structure and other characteristics of impurities and intermediaries, if any

CHECKS ON API

- Sampling techniques
- General features
- Analytical methods

v Physical tests

v Identification tests

v Tests of purity

v Evaluation methods

- Validation of analytical methodologies
- Specifications
- Justification of specifications
- Elucidation of structure and other characteristics
- Test protocols of three batches

If product control methods are codified, please indicate the Pharmacopoeia in which they appear.

REFERENCE MATERIALS/STANDARDS

Requirements in accordance with Annex 4 of ANMAT Order No 2819/04

PACKAGING AND PACKING MATERIAL

- Description
- Physical-chemical and functional checks
- Specifications
- Justification of specifications

STABILITY

- Number of batches examined
- Environmental conditions under which examination took place
- Description of final packaging
- Test method
- Validation of test method

- Frequency of checks
- Designated lifespan and method of preservation. Frequency of additional checks
- Summary of report – Conclusions
- Post-registration stability protocol
- Stability data

For all items, provide documentation supporting the tests performed and facilitating traceability of the information.

SIGNATURE

SIGNATURE

OWNER/LEGAL REPRESENTATIVE

TECHNICAL MANAGER: