MINISTRY OF HEALTH
SECRETARY OFFICE OF POLICIES, REGULATIONS AND INSTITUTES
A.N.M.A.T

REGULATION 7075

BUENOS AIRES, OCTOBER 14, 2011

HAVING SEEN Act 16.463, as regulated by Executive Orders 9763/64, 150/92 (1993 Revised Text), Executive Orders 1490/92 and 341/92 as well as File 1-47-1110-379-11-1 of the Registry of this Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (Argentine Food, Drugs and Medical Technology Administration); and

CONSIDERING:
That section 1 of Act 16.463 establishes that “the import, export, manufacturing, fractionation, commercialization or storage in Argentine jurisdiction or intended to inter-provincial commerce, of drugs, chemical products, reagents, dosage forms, medicines, diagnostic elements, and any other product to be used and applied to human medicine, as well as the physical or legal persons participating in such activities, are subject to this act and to the regulations to be passed pursuant thereto”.

That section 2 of the previously mentioned act establishes that the indicated activities shall only be performed with the prior authorization and under the monitoring of the health authority, in manufacturing facilities authorized by it and under the technical management of the relevant university professional; and also in the terms and pursuant to the rules established by the regulation, taking into consideration the particular features of each activity and reasonable technical guaranties in order to protect public health and the economy of consumers.

That moreover, section 3 of such act establishes that products therein comprised shall meet the conditions established in the Argentine Pharmacopoeia (Farmacopea Argentina), and if not appearing therein, those conditions resulting from international patterns and from texts with acknowledged scientific value, and such products shall be registered with this Administración Nacional pursuant to provisions of Executive Order 150/92 (1993 Revised Text).

That Section 1 of Executive Order 9763/64, regulating Act 16463 establishes that the exercise of police power in health referred to the activities indicated in Section 1 of such act, and to the physical and legal persons participating in such activities, shall be performed by the Argentine Ministry of Social Work and Public Health (currently Health Ministry), in the jurisdictions therein indicated.

That, moreover, Executive Order 1490/92 creates this Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (ANMAT), as a decentralized agency with respect to the National Public Administration, with a financial and economic autarchic regime, with jurisdiction over the whole territory of Argentina, to undertake such tasks.

That pursuant to section 3, paragraph a) of the previously mentioned executive order, this National Administration acts, among other, in everything related to the control and monitoring of health and of the quality of drugs, chemical products, reagents, dosage forms, medicines, diagnostic elements, biomedical materials and technologies and any other product to be used in or applied to human medicine.

That this National Administration is the drugs regulatory authority and is authorized to grant the health registration of drugs, pursuant to the requirements and procedures established in each case.

That Executive Order 150/92 (1993 Revised Text), regulating Act on Drugs 16463, established a series of definitions, rules and procedures that constitute the basis supporting everything related to the registration, manufacturing, fractionation, dispensation, commercialization, export and import of medicines and medicinal products.

That pursuant to provisions of such Executive Order, a medicine is “any pharmaceutical preparation or product used for the prevention, diagnosis and/or treatment of a disease or pathologic condition, or to modify physiological systems in the benefit of the person to whom it is administered” (section 1 paragraph a).

Moreover, paragraph b) of such section defines as active substance or drug substance “every chemical substance or mix of related substances, either natural or synthetic, which having a specific pharmacologic effect, is used in human medicine”.

That also paragraph c) defines generic name as “name of an active substance or drug substance or, when appropriate, an association or combination of active substances at fixed dosage, as adopted by the national health authority, or, if not, the international non-proprietary name of an active substance, recommended by the World Health Organization”.

That finally paragraph d) defines medicinal product as “every medicine, designated by a conventional name, whether or not the trademark or trade name, or by the generic name corresponding to its composition and content, consistently prepared and packaged for its distribution and sale, having a defined, stated and verifiable quantitative composition, with a stable dosage form and with verifiable therapeutic action”.

That the concept of medicine comprises, among other, synthetic, semi-synthetic and biological medicines, the difference of which is that the latter are composed of proteins, nucleic acids, sugars or a complex combination of these substances or they are living substances such as cells or tissues or are derived therefrom, capable of being isolated from a variety of natural sources of human or animal origin or microorganisms, or obtained by biotechnological methods or by other technologies, being their characterization more complex, thus requiring a more detailed description of their structure and manufacturing process.

That taking into account the above, it is necessary to pass specific rules establishing scientific and technical requirements and particular formalities for the registration of biological products, as amended, with the purpose of effectively evidencing their quality, efficacy and safety.

That from the operational viewpoint, it is deemed convenient to adopt the management modality described in ANMAT Regulation 5755/95, or the one replacing it in the future, for which purpose a specific form has been prepared for the processing of registration applications in the registry of biological products.

That the Department of Legal Affairs has participated as relevant.

That this regulation is issued pursuant to the powers conferred by Executive Order 1490/92 and by Executive Order 425/10.

Therefore,

THE DEPUTY HEAD (INTERVENTOR) OF ADMINISTRACIÓN NACIONAL DE MEDICAMENTOS, ALIMENTOS Y TECNOLOGÍA MÉDICA

HEREBY RESOLVES:

SECTION 1: The requirements and demands for the registration of biological medicinal products are hereby established, included in Annex I hereof and are an integral part of this Regulation.

SECTION 2 – Biological medicinal products for human use, industrially manufactured or in the manufacturing of which there is an industrial process, are comprised within this regulation, to wit:

- Blood derivatives
- Products obtained from recombinant DNA
- Monoclonal antibodies
- Biological medicines obtained from animal biological fluids or tissue
- Other biological products

SECTION 3 – Vaccines regulated by ANMAT Regulation 705/05, as amended and/or supplemented, products not requiring registration with the REM such as advanced therapy medicinal products completely manufactured at a specialized center authorized thereto by the competent health authority, to be exclusively used at and by such center pursuant to conditions determined by such health authority, individualized allergenic vaccines and human whole blood, plasma and blood cells and their components, are excluded from this regulation.

SECTION 4 – The procedures for the admission, evaluation and validation of registration applications in the registry of biological medicinal products are hereby established. Such procedures appear in Annex II hereof and are an integral part of this regulation.

SECTION 5 – The Table of Contents and Form for the Registration Application of Biological Medicinal Products in the Registry of Medicinal Products (REM as per its Spanish Acronym), of this National Administration, are hereby approved, the format and content of which appear in Annex III hereof, and are an integral part of this regulation.

SECTION 6 – The registration certificate of biological medicinal products shall contain, at least, the following information

a) identification number of the certificate
b) name of product
c) dosage form
d) how supplied
e) registration number of the medicinal product
f) registration date in the registry
g) expiration date in the registry
h) composition (includes quality references)
i) shelf-life
j) storage conditions
k) registration holder, country
l) manufacturer(s), country of the active pharmaceutical ingredient (API), intermediates, semi-manufactured products and finished products
m) indications
n) contraindications
o) precautions
p) warnings
q) technical summary of product

SECTION 7 The registration application with the REM of a biological medicinal product may be denied in the following cases, yet not limited to such cases:

a) when the benefit-risk ratio is not favorable;
b) when the therapeutic efficacy is not sufficiently justified;
c) when the medicine does not have a declared qualitative and quantitative composition, or when it lacks adequate quality;
d) when the data and information contained in the documents supplied by applicant in the registration application file and/or obtained during the verifications performed by this Administration in the course of the evaluation process, are erroneous, do not comply with current regulations, are inconsistent and/or do not support what is claimed;
e) In every other case in which this National Administration deems it relevant based on public health considerations.

SECTION 8 – It is hereby established that once the registration is granted and the marketing licensing of the biological medicinal product obtained in accordance with the

current regulations, the registration holder and its technical director, as well as manufacturers participating in the manufacturing process, as applicable, and their respective technical directors, shall be jointly and severally liable for the compliance with the provisions established in this regulation.

SECTION 9 – Non compliance with the obligations established in this regulation shall make infringers subject to the penalties established in Act 16463 and Executive Order 341/92, notwithstanding other applicable actions.

SECTION 10 – The Glossary of terms appearing in Annex IV of this regulation is hereby approved and it is an integral part hereof.

SECTION 11 – This National Administration shall prepare the Supplementary Guides necessary for the effective implementation of this regulation.

SECTION 12 – It is hereby established that the registration applications of biological medicinal products with the REM shall pay a fee of PESOS TEN THOUSAND (ARS 10,000).

SECTION 13 – This National Administration shall decide on the registration applications of biological medicinal products with the REM within a term of ONE HUNDRED AND EIGHTY (180) administrative business days, counted as from the notice regarding the validation of the application submission in accordance with provisions of Annex II hereof.
This Administration shall be able to issue its decision in a shorter term than the one provided for in the previous paragraph, in the event of public health considerations that so require.

SECTION 14 – The management modality established in Regulation ANMAT 5755/97 or in the Regulation that may replace it in the future, is hereby adopted.

SECTION 15 – This provision shall enter into force as from the day following its publication in the Official Gazette.

SECTION 16 – Be it registered and communicated to whom it may concern. Be it notified to CAEME, CILFA, COOPERALA, CAPGEN, COFA and other entities representing the industry. Be it delivered to the National Department of Official Registry for its publication. Upon completion, be it permanently filed.

File 1-47-1110-379-11-1
ANMAT REGULATION 7075

SIGNED: DR. CARLOS A CHIALE – DEPUTY HEAD - ANMAT

ANNEX I
REQUIREMENTS AND FORMALITIES FOR THE REGISTRATION OF BIOLOGICAL MEDICINAL PRODUCTS

DOCUMENTS FOR PRODUCT REGISTRATION

In order to request the registration of a biological medicinal product, the following documents and information must be submitted, organized with a table of contents of the presentation, form and five chapters, which shall constitute the registration file of the medicinal product.

In a supplementary way, this Administration shall establish particular and specific requirements to be complied by products obtained through recombinant DNA, monoclonal antibodies, allergen vaccines, blood derivatives and others so requiring, besides those provided for in this regulation.

CHAPTER I: Administrative Data and Indications.

CHAPTER II: Summaries corresponding to the presentations of Chapters:
III- Quality Information: Physicochemical – Pharmaceutical and Biological Information, IV – Preclinical Information and V – Clinical Information

CHAPTER III Quality Information: Physicochemical – Pharmaceutical and Biological Information
of the Active Pharmaceutical Ingredient
of the Medicine.

CHAPTER IV: Preclinical Information

CHAPTER V: Clinical Information

CHAPTER I. ADMINISTRATIVE DATA AND INDICATIONS

Table of Contents

The table of contents corresponding to all the documents submitted, notwithstanding that each chapter is submitted with its specific table of contents, shall be included.

1. General Data of Applicant and Manufacturer/s

The applicant of a marketing authorization for a biological medicine must be established in Argentina and authorized by this Administration.

The following data and information, both of applicant and of manufacturer/s, must be supplied, to wit:

a) Name, domicile and type of applicant.

b) Name and domicile of manufacturer/s. When more than one manufacturer participates in the manufacturing of the active pharmaceutical ingredient/s, intermediate, semi-manufactured and/or finished products, the following must be indicated: name and domicile for each of them, responsibility and contractual relationship for each manufacturing stage, and the corresponding legal documents evidencing the relationships declared and that such relationships have been legally established must be attached.

c) Authorization of applicant and of the manufacturing facilities for active pharmaceutical ingredient/s, intermediate products and finished products. For manufacturers based abroad, a Certificate of Compliance with Good Manufacturing Practices issued by a competent Health Authority must be submitted, together with the corresponding authorization issued by this Administration.

d) Documents issued by the Health Authority of the country of origin evidencing its authorization and effective marketing and/or effective authorization and marketing documents issued by other Health Authority/ies. It must be indicated if the medicinal product is in process of registration at the time of submission of the authorization application.

2. Data of Proposed Certificate Holder

3. Summary of Product Characteristics

3.1 Name of medicinal product (brand name)
3.2 Name of active pharmaceutical ingredient/s
3.3 Dosage form/s
3.4 Route/s of administration
3.5 Pharmacological classification
3.6 ATC Code/s
3.7 Proposed indications
3.8 Potency, strength or dose per dosage unit
3.9 Complete formula per dose, unit of dosage form or percentage, including excipients
3.10 Origin of active pharmaceutical ingredient/s
3.11 Brief description of the source of the active pharmaceutical ingredient/s
3.12 Dosage form/s including primary and secondary package/s both for retail sale and hospital use
3.13 Content per unit of sale
3.14 Shelf life and proposed conditions of preservation for the non-reconstituted and reconstituted product, for the latter if applicable (temperature range, influence of humidity and light sensitivity)
3.15 Proposed dispensation condition
3.16 Use restrictions
3.17 Therapeutic action
3.18 Pharmacodynamic, pharmacokinetic and toxicological properties
3.19 Indications
3.20 Contraindications
3.21 Warnings and precautions
3.22 Use during pregnancy and breastfeeding
3.23 Interactions and incompatibilities
3.24 Side effects
3.25 Poisoning, symptoms, urgency treatment and antidotes
3.26 Way of preparation
3.27 Dosage
3.28 Primary package labels
3.29 Secondary package labels
3.30 Package Insert

CHAPTER II. SUMMARIES OF THE CHAPTERS REGARDING TECHNICAL DOCUMENTS

- Table of Contents
- Introduction
- Quality Information Summary
- Summary of Preclinical Studies Information
- Summary of Clinical Studies Information
- Annexes

A. At the time of commencement of the registration formality, applicant should submit a brief description of the facilities and equipment involved in the manufacturing of the product.
B. Safety evaluation regarding foreign/external agents. Drugs containing or using materials of animal and/or human origin in the manufacturing process (procedure regarding transmissible spongiform encephalopaties (TSE)).
C. Bibliographical references.

CHAPTER III. QUALITY INFORMATION. PHYSICOCHEMICAL-PHARMACEUTICAL AND BIOLOGICAL INFORMATION

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PHARMACEUTICAL DEVELOPMENT

The information corresponding to the development studies performed to establish that the dosage form, formulation and its components, manufacturing process, packages, closing system/s of package, microbiological attributes, proposed shelf-life and use instructions are adequate for the intended use specified in the authorization application file, must be available for verification by this Administration during the registration stage, as well as the documents and information corresponding to pilot batches.

COMPOSITION

Qualitative and quantitative composition of the medicinal product, per unit of dosage form or percentage (weight or volume) including active pharmaceutical ingredients and other raw materials, as well as components that though not present in the finished product were used in its manufacturing, indicating those lost during the process. The function of each substance in the formulation must be specified.

ACTIVE PHARMACEUTICAL INGREDIENT (A.P.I.)

General information on the active pharmaceutical ingredient/s and intermediate products as applicable.

- *Brief description of the manufacturing process and packaging*

A manufacturing flow chart must be included, indicating process controls and when more than one manufacturer participates, indication of the stage in which each manufacturer participates.

This brief description must highlight quality control parameters of the process, specifications and references to analytical methods.

There follows a general indication regarding the information to be submitted:

a) Starting materials such as animal or vegetal tissues, fluids, microorganisms, strains, cell lines, plasma or blood components and genetically modified multicellular organisms. Other biological materials used such as cell substrates, culture media, monoclonal antibodies, enzymes, among other, including source, origin and quality specifications and detection of adventitious agents as applicable.
b) For animal and/or human origin components, the absence of foreign/strange agents or the ability to eliminate or reduce them during the manufacturing

process (procedure regarding transmissible spongiform encephalopaties (TSE) or other infectious agents), must be evidenced.

c) Acceptance or rejection criteria of eventual reprocesses for each stage.
d) Description of filling and closing procedures for the A.P.I. finished product or intermediate product. Conditioning procedures.
e) Description of cold chain procedures used. In the event of different laboratories, information regarding actions taken for the transfer of the material from one site to another must be included.
f) Demonstration of manufacturing consistency.

Results of tests must be submitted for a minimum of three batches with a batch size corresponding to routine production scale batches or batches that may be scaled up to such size, taking into account that for the latter, the change of scale should not affect the quality, safety and efficacy attributes.

- *Quality Specifications*

When the quality specification is from the Argentine Pharmacopoeia or from internationally acknowledged pharmacopoeias, such document shall be listed indicating specifications and limits applied together with acceptance/rejection criteria.

If not included in the Argentine Pharmacopoeia or in internationally acknowledged pharmacopoeias, the information related to the quality specification must be submitted, to wit: physicochemical, biochemical and immunological characterization of the active biological pharmaceutical ingredient, purity and impurity profile, full description of analytical methods and their limits and acceptance/rejection criteria, standards used and their corresponding validation.

Description of specifications, acceptance methods and criteria for packaging materials in direct contact with the product.

Raw materials: in the cases in which quality specification corresponds to official pharmacopoeias, the specifications and acceptance limits shall be listed. For excipients not appearing in official pharmacopoeias, apart from the previous requirement, a full description of the analytical method shall be submitted.

For animal and/or human origin components, apart from the previously indicated requirements, the absence of foreign/strange agents or the ability to eliminate or reduce them during the manufacturing process (procedure regarding transmissible spongiform encephalopaties (TSE) or other infectious agents), must be evidenced.

- *Stability*

Stability studies corresponding to active pharmaceutical ingredients in the proposed storage and packaging conditions shall be submitted pursuant to the current regulations on these issues.

FINISHED PRODUCT

MANUFACTURING

a) Manufacturing formula, including batch size.
b) Manufacturing:

- A manufacturing flow chart must be included, indicating process controls and stages in which other manufacturing facilities participate. This description must highlight quality control parameters of the process and analytical methods used.
- Full description of the whole process, manufacturing methods and their corresponding controls.
- Description of equipment, premises and facilities.
- For in process-product, when applicable, specifications, limits and description of analytical methods used, for each stage of the manufacturing process, shall be included.
- Description of filling and closing procedures for finished or intermediate product. Conditioning procedures.
- Description of procedures applicable to cold chain maintenance. If applicable, include procedures or instructions regarding actions, conditions and precautions taken for the transfer of materials to different sites.
- For animal and/or human origin components, the absence of foreign/strange agents or the ability to eliminate or reduce them during the manufacturing process (procedure regarding transmissible spongiform encephalopaties (TSE) or other infectious agents), must be evidenced.

c) Demonstration of manufacturing consistency.

- Results of tests must be submitted for a minimum of three batches with a batch size corresponding to routine production scale batches or batches that may be scaled up to such size, taking into account that for the latter, the change of scale should not affect the quality, safety and efficacy attributes.

  Batches must have been prepared with different bulk active pharmaceutical ingredients. If this is not possible, such situation must be explained and grounded.

- Information corresponding to the Summary Manufacturing Protocol and Control thereof.

- *Control Methods*

Quality Specifications

a) Finished Product

In case of specifications determined by the manufacturer, information regarding same must be submitted, full description of analytical methods and their limits and acceptance/rejection criteria, reference standards or materials used, and their corresponding validation.

If the quality specification is from the Argentine Pharmacopoeia or from internationally acknowledged pharmacopoeias, it shall be described indicating specifications and limits applied together with acceptance/rejection criteria.

b) Excipients

Specifications and limits shall only be indicated when the quality reference does not correspond to official pharmacopoeias. For excipients not appearing in official pharmacopoeias used for the first time in medicinal products, apart from the previous requirement, a full description of the analytical method shall be submitted.

c) Packaging materials in direct contact with the product

Specifications, acceptance methods and criteria shall be described.

Remarks

The quality specifications mentioned shall be submitted in the form of a table and independently of the analytical methods, indicating acceptance/rejection criteria with their tolerance ranges. When applicable, the confidence interval of the test must be specified.

The analytical methods shall be described in detail so that the procedure may be replicated at the analysis laboratory.

If quality specifications correspond to the manufacturer, their identification through acronyms, numbers or another adequate coding system must be included.

REFERENCE MATERIALS

The description and characterization of reference standards / preparations must be submitted.

STABILITY STUDIES

Stability studies corresponding to active pharmaceutical ingredients and to finished products in the proposed storage and packaging conditions, shall be submitted pursuant to current regulations.

INFORMATION ON VALIDATIONS OF PROCESSES, REPROCESSES AND NON-CODED ANALYTICAL METHODS

Information on the validation of processes, reprocesses and analytical methods used must be included. In the case of the latter, when they are own non-coded methods.

ANNEXES

A. Brief description of the facilities and equipment involved in the manufacturing of the product.
B. Safety evaluation regarding foreign/external agents. Medicines containing or using materials of animal and/or human origin in the manufacturing process (procedure related to transmissible spongiform encephalopaties, TSE).
C. Bibliographical references.

CHAPTER IV. PRECLINICAL INFORMATION

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2. Preclinical information to be submitted must conform to all the requirements established by current regulations on the Regime of Good Research Practices in Clinical Pharmacology Studies and it must also take into account the following considerations for toxicity studies:

2.1. Although as a general rule, toxicity studies must be performed in two relevant animal species adequate to the nature of this kind of products, in certain cases the selection of one species shall be sufficient (when only one relevant species is found or in long-term studies).

In cases where not even one relevant species is found, the use of transgenic animals expressing the human receptor or the use of homologous proteins may be considered. Finally, in case of not being able to comply with the above mentioned requirements, the performance of a repeated dose study on a single species for a period to be defined according to the product under study shall be recommended, evaluating specific functions and morphology (e.g.: cardiovascular, respiratory, among others).

2.2. Toxicological evaluation of contaminants and impurities

2.3. When deemed convenient due to the characteristics of the product under study, antigenicity (e.g. anti-product antibodies) and immunotoxicity (e.g. for products proposed to stimulate or suppress the immune system) reactions must be determined.

3. BIBLIOGRAPHICAL REFERENCES.

CHAPTER V. CLINICAL INFORMATION

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2. CLINICAL INFORMATION

Considering that it is necessary to specify the scientific and technical requirements to demonstrate the efficacy and safety of the product to be registered, the studies submitted must evidence:

- The pharmacological properties of the product as related in quantitative and qualitative form with the therapeutic indication/s intended to be registered.
- The pharmacological efficacy and the relative safety on humans so that the benefit/risk equation of the clinical indications proposed is favorable to the patient.

Study results shall be submitted separately together with a summary thereof, also including non completed studies.

Final reports with detailed description of the main aspects of the protocol and the analytical methods used shall be included, highlighting the research design and compliance with current Good Clinical Practices:

- Characteristics of the population studied
- Results in terms of efficacy (it includes clinical and biological evaluation, main efficacy criterion and other criteria)
- Clinical and biological results regarding safety
- Statistical evaluation of results
- Submission of clinical and laboratory results in the form of a table
- Discussions and conclusions
- Annexes
- Individual data of patients
- Information about immunogenicity

The clinical studies performed must support the product pharmacokinetics, pharmacodynamics, safety and efficacy. They must be performed according to current regulations.

Clinical studies must include: Phase I pharmacological studies evidencing tolerance and the pharmacokinetics profile in human beings. Phase II clinical pharmacological studies effectively evidencing therapeutic activity as well as the occurrence and magnitude (incidence and severity) of adverse events. Phase III pharmacological studies evidencing compared therapeutic efficacy (parallel group clinical trial) in a significant quantity of patients, with proper information regarding quality and quantity of observed adverse events.

POST-MARKETING INFORMATION

It comprises the procedure through which companies and public vigilance networks generate information reported to the Health Authority about the efficacy and specifically about the safety of the biological medicinal product, including those of biotechnological origin, resulting from spontaneously reported experience and/or through Phase IV clinical trials.

Post-marketing evaluation requires the implementation of an integral system to collect reports, epidemiological analysis, risk evaluation and management and detailed report and information procedures, enabling the manufacturing or importing pharmaceutical company of a biological or biotechnological product, to control the efficacy and safety profile of the product during its life cycle.

In this sense:

a) periodic safety reports allowing a proper safety evaluation over time must be submitted to this Administration.

b) during the registration stage of the medicinal product, applicant shall submit the post-marketing vigilance plan defined.

c) for an effective post-marketing monitoring, the biological/biotechnological medicinal product shall be clearly identified.

d) during the marketing of the medicinal product, the Registration Holder shall report to this Administration the occurrence of unforeseen adverse events/effects related to the drug that could restrict its use. In this sense, the pharmacovigilance system and the established risks management plan must be described in detail, and there must be a document evidencing the existence of the necessary infrastructure and of a qualified person in charge of pharmacovigilance in Argentina for proper reporting of any suspected or real adverse reaction occurring in Argentina or in a third country.

e) when post-marketing studies are performed, the information about them must include:

a. Number of exposed patients.

b. Evaluation of adverse reactions and of reports thereof

c. Study of the influence of physiopathological factors

d. Impact studies on the National Health System, if applicable

PUBLISHED AND NON-PUBLISHED STUDIES

Published and non-published studies about ongoing trials and completed trials shall be submitted, including any safety information obtained, as well as any other kind of information.

BIBLIOGRAPHICAL REFERENCES

ANNEX II

PROCEDURES FOR THE ADMISSION, VALIDATION AND EVALUATION OF APPLICATIONS FOR THE REGISTRATION OF BIOLOGICAL MEDICINAL PRODUCTS BEFORE REM (REGISTRATION OF MEDICINAL PRODUCTS)

I. PROCEDURE FOR THE ADMISSION AND VALIDATION OF THE APPLICATION

This Administration shall establish the flow chart for the evaluation of the applications.
Upon receiving the application, the corresponding area of this Administration shall verify that the application meets the general requirements to commence with the evaluation.
In case that the application does not meet the established requirements, the applicant shall be requested to cure the deficiencies in the terms established and according to the procedures included in the current Argentine Administrative Procedures Act, as regulated.

II. PROCEDURE FOR THE EVALUATION OF DOCUMENTS SUBMITTED FOR THE REGISTRATION APPLICATION BEFORE REM

Once the application is admitted, the areas appointed by this Administration shall perform an evaluation of the documents submitted and shall issue the corresponding report. To such purpose, the submission of supplementary documents and clarifications about any issue in the application may be requested to the applicant.
This National Administration, through the corresponding areas, shall conduct procedures for the verification of the documents submitted, during the evaluation stage, which may include inspections to the manufacturing facilities involved in the manufacturing process/es and control of the medicinal product under evaluation, and even to the manufacturing facilities of the pharmaceutical active ingredient.
In the above mentioned cases, the terms established for the evaluation of the file shall be suspended until the supplementary information required is submitted and/or obtained.
Once the documents are evaluated and in case of a favorable report, this Administration shall issue the corresponding authorization.

III. EFFECTIVE MARKETING

Once the authorization certificate of the biological medicinal product is obtained, the authorization holder shall expressly notify this Administration the decision to initiate the marketing of the authorized product, pursuant to the provisions of the current regulations regarding the marketing authorization for the first batch.

ANNEX III

ANMAT (National Food, Drug and Medical Technology Administration)	**REGISTRO DE ESPECIALIDADES MEDICINALES** **REM** **(Registry of Medicinal Products)** **REGISTRY OF BIOLOGICAL MEDICINAL PRODUCTS**	**1.2. BIO**

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	4.2.1.2.	Evidence of absence of foreign/external agents or the ability to eliminate or reduce them during the manufacturing process.	
	4.2.1.3.	Acceptance or rejection criteria of eventual reprocesses	
	4.2.1.4.	Description of filling and closing procedures for the A.P.I.	
	4.2.1.5	Description of filling and closing procedures for the intermediate product	
	4.2.1.6.	Conditioning procedures	
	4.2.1.7.	Cold chain maintenance procedures	
	4.2.1.8.	Demonstration of manufacturing consistency	
	4.3.	QUALITY SPECIFICATIONS	
	4.3.1	A.P.I. quality specifications	
	4.3.2.	Physicochemical, biochemical and immunological characterization of A.P.I.	

	4.3.3.	Purity and impurity profile	
	4.3.4.	Description of analytical methods, their limits, acceptance/rejection criteria, standards used and corresponding validation.	
	4.3.5.	Quality specifications of packaging in direct contact with the product	
	4.3.6.	Quality specifications of raw materials/excipients	
	4.4.	STABILITY	
	5.	**FINISHED PRODUCT**	
	5.1.	MANUFACTURING	
	5.1.1.	Manufacturing formula, including batch size	
	5.1.2.	Manufacturing	
	5.1.2.1.	Manufacturing flow chart	
	5.1.2.2.	Description of the whole process, manufacturing methods and their controls	
	5.1.2.3.	Description of the equipment, premises and facilities	
	5.1.2.4.	For in-process product: specifications, limits and description of the analytical methods for each stage of the manufacturing process	
	5.1.2.5.	Description of filling and closing procedures for the finished or intermediate product	
	5.1.2.6.	Conditioning procedures	
	5.1.2.7.	Cold chain maintenance procedures	
	5.1.2.8.	Evidence of absence of foreign/external agents or the ability to eliminate or reduce them during the manufacturing process.	
	5.1.2.9.	Demonstration of manufacturing consistency	
	5.2.	CONTROL METHODS	
	5.2.1.	Quality specifications for the finished product	
	5.2.2.	Quality specifications for excipients	
	5.2.3.	Quality specifications of packaging materials in direct contact with the	

		product	
	5.2.4.	REFERENCE MATERIALS	
	5.2.5.	STABILITY	
	6.	**REFERENCE MATERIALS**	
	7.	**STABILITY STUDIES**	
	8.	**INFORMATION ABOUT VALIDATIONS OF PROCESSES, REPROCESSES AND NON-CODED ANALYTICAL METHODS**	
	9.	**ANNEXES**	
	9.1.	Description of the facilities and equipment involved in manufacturing	
	9.2.	Safety evaluation regarding foreign/external agents. Drugs containing or using animal and/or human origin materials in the manufacturing process.	
	9.3.	Bibliographical references	

A.4. CHAPTER IV. PRECLINICAL INFORMATION

	1.	**TABLE OF CONTENTS**	
	2.	**PRECLINICAL STUDIES**	
	3.	**BIBLIOGRAPHICAL REFERENCES**	

A.5. CHAPTER V. CLINICAL INFORMATION

	1.	**TABLE OF CONTENTS**	
	2.	**CLINICAL STUDIES**	
	3.	**POST-MARKETING INFORMATION**	
	4.	**PUBLISHED AND UNPUBLISHED STUDIES**	
	5.	**BIBLIOGRAPHICAL REFERENCES**	

A.6. DOCUMENTS TO BE ATTACHED

	1.	**Fee payment voucher**	
	2.	**Copy of authorization certificate of own manufacturing and quality control laboratory/ies, issued by ANMAT for the activity declared for manufacturing plants located in Argentina.**	
	3.	**Copy of authorization certificate of the contracted laboratory/ies, for the activity declared.**	
	4.	**Copy of the authorization document as a representative of a foreign company, if applicable.**	
	5.	**Copy of the contracted manufacturing and quality control laboratory/ies for the declared activity, pursuant to current GOOD MANUFACTURING PRACTICES.**	
	6.	**Good Manufacturing Practices certificate issued by the Health Authority of the country of origin for the manufacturing plant/s and/or third parties involved.**	
	7.	**Good Manufacturing Practices certificate issued by ANMAT with the corresponding supporting Regulation**	
	8.	**Copy of authorization certificate of country of origin for medicinal products that already have marketing authorization.**	
	9.	**List of countries in which the medicinal product is already registered and commercialized in the case of medicinal products that are already being commercialized.**	
	10.	**Information on whether the medicinal product to be registered is already undergoing a registration process before another Health Authority (indicate status) and/or whether its authorization has been denied.**	
	11.	**Draft Labeling**	
	12.	**Draft Package Inserts**	

B. FORM 1.2. BIO

APPLICATION FOR THE REGISTRATION OF BIOLOGICAL MEDICINAL PRODUCTS

CHAPTER I – ADMINISTRATIVE DATA AND INDICATIONS

1. DATA OF APPLICANT

Type: (mark corresponding option)

Pharmaceutical company: ☐

Representative of foreign company: ☐

1. 2. Name or Corporate Name:

1. 3. File No.:

1. 4. Registered Domicile:

Street and number:
Location:
Zip Code:
Province:
Telephone:
Fax:

1. 5. Technical Management:
Technical Director or Co-Director,
signing the application:
Last Name and First Name:
ID (D.N.I) No:
Professional License No.:

1. 6 Legal Represent. or Attorney-in-fact,
signing the application

Last Name and First Name:

ID (D.N.I.) No.:

2..	DATA OF PROPOSED CERTIFICATE HOLDER

2. 1 Name or Corporate Name:

2. 2 Registered Domicile:

Street and Number:

Location:

Zip Code:

Province:

Country:

Telephone:

Fax:

3..	SUMMARY OF PRODUCT CHARACTERISTICS AND INDICATIONS

3. 1. Trade Name:

3. 2 . Name of the Active Pharmaceutical Ingredients

3.3. Dosage Form/s

3.4. Route/s of administration

3.5. Pharmacological classification

3.6. ATC Code/s

3.7. Proposed indications

3.8. Power, concentration or dosage per unit

Power, concentration or dosage per unit

3.9. Complete formula per dose, unit of dosage form or percentage, including excipients:

Active Ingredient/s Nonproprietary Name	Content	UNIT OF MEASURE

EXCIPIENTS	PAHO Code	Content per unit of dosage form	UNIT OF MEASURE

3.10. Origin of Active Pharmaceutical Ingredient/s:

Biological: ☐

Biotechnological: ☐

Other: ☐

3.11. Brief description of source of Raw Material/s:

3.12. Pack including primary and secondary packages both for retail sale and hospital use

3.13. Content per unit of sale:

3.14. Shelf life, proposed preservation conditions for the non-reconstituted and reconstituted product, for the latter, if applicable (temperature range, influence of humidity and light sensitivity)

3. 15 Proposed Sales Condition:

3.16. Use restrictions:

Professional use only: ☐

Institutional use only: ☐

3.17. Therapeutic action

3.18 Pharmacodynamic, pharmacokinetic and toxicological properties

3.19. Indications

3.20.Contraindications

3.21. Warnings and precautions

3.22. Use during pregnancy and breastfeeding

3.23. Interactions and incompatibilities

3.24. Side effects

3.25. Poisoning, symptoms, urgency treatments and antidotes

3.26. Way of preparation

3.27. Dosage

3.28. Primary package label

3.29. Secondary package label

3.30. Package insert

4	DATA OF MANUFACTURING FACILITY/IES

4. 1.- Manufacturer of Active Ingredient/s (*)

Corporate Name:

Authorization Certificate No.:

Name of Technical Director:

Address:

Street and number:

Province:

Location:

Zip Code:

Telephone:

Fax:

4. 2. Manufacturer of Finished Product (*)

Corporate Name:

Authorization Certificate No.:

Name of Technical Director:

Address:

Street and number:

Province:

Location:

Zip Code:

Telephone:

Fax:

4.3. Other plants that participate in the manufacturing process: (*)

Corporate Name:

Authorization Certificate No.:

Name of Technical Director:

Address:

Country:

Street and number:

Province:

Location:

Zip Code:

Telephone:

Fax:

4.4. Quality Control Laboratory (*)

Corporate Name:

Authorization Certificate No.:

Name of Technical Director:

Address:

Country:

Street and number:

Province:

Location:

Zip Code:

Telephone:

Fax:

(*) Repeat for each stage performed by different facilities

ANNEX IV
GLOSSARY OF TERMS

Biological Medicines: Are products obtained from living organisms or their tissues. They include viruses, therapeutic sera, toxins, antitoxins, vaccines, blood, blood components or derivatives, allergenic products, hormones, colony-stimulating factors, cytokines, antibodies, heparins, among other. Manufacturing sources and methods comprise, though not limited to, cell culture, microorganisms, extraction from biological tissue or fluids, recombinant DNA techniques, transgenesis, hybridoma techniques, propagation of microorganisms in embryos or animals, etc. They are products used for purposes of prevention, treatment or *in vivo* diagnosis of certain diseases.

Biotechnological Medicinal Products or Medicines: For the purposes of this regulation, biotechnological medicinal product or medicine is any product the active pharmaceutical ingredient of which is obtained through the use of live organisms or cells by means of Recombinant DNA and/or Hybridoma Techniques.

Blood Derivative Medicinal Products or Medicines: Medicinal Product or Medicine resulting from blood components industrially prepared. They include, among other, albumin, clotting factors and human immunoglobulins.

Immunologic Medicines: Sera, vaccines, toxins and allergens, including individualized vaccines for a specific patient.

Immune Serum: agent used to produce passive immunity.

Vaccines: preparations containing antigenic substances capable of inducing an active and specific immunity in humans against an infectious agent, its toxins or the antigens made by such agent (Regulation ANMAT 705/05).

Toxins / Toxoids: agents used to diagnose the immune status or in immunomodulator therapies.

Allergenic Product: any medicinal product which is intended to identify or induce a specific acquired alteration in the immunological response to an allergizing agent

Vaccines of individualized allergens: those vaccines prepared with immunizing agents, at a specific concentration and dilution based on the corresponding medical prescription for a patient.

Advanced Therapy Medicinal Products:
Shall be any of the following products to be used in human beings:

d) Gene therapy medicinal product: product obtained through a set of manufacturing processes with the purpose of transferring, in vivo or ex vivo, a prophylactic, diagnostic or therapeutic gene (i.e., a bit of nucleic acid) to human/animal cells and its further expression in vivo).

e) Somatic cell therapy medicinal product: for the purposes of this regulation, a somatic cell therapy medicinal product is the use in human beings of live somatic cells, both autologous (coming from the patient itself), as allogeneic (from another human being) or xenogeneic (from animals), the biological features of which have been substantially altered as a result of their manipulation to obtain a therapeutic, diagnostic or preventive effect through metabolic, pharmacologic and immunologic means. Such manipulation includes expansion or activation of autologous cell populations ex-vivo, the use of allogeneic or xenogeneic cells associated to medical products used in vivo or ex vivo.

f) Tissue engineered product is defined as the one containing or formed by cells or tissue manipulated by engineering and which allegedly has properties, is used or administered to persons in order to regenerate, restore or replace human tissue. A tissue engineered product may contain cells or tissues of human or animal origin, or both. Cells or tissues may be viable or not. It may contain other substances as cell products, biomolecules, biomaterials, chemical substances, supports or matrices.