MINISTRY OF HEALTH

ARGENTINE ADMINISTRATION OF FOOD, DRUGS AND MEDICAL TECHNOLOGY (ANMAT)

Provision No. 4008/2017

Buenos Aires, April 26, 2017

By virtue of ANMAT Provision No. 6677/10 and File No. 1-0047-0000-003833-17-2 of the ANMAT Registry, and

CONSIDERING THAT:

ANMAT Provision No. 6677/10 approved the Good Clinical Practice Regime for Clinical Pharmacology Studies for the primary purpose of guaranteeing and ensuring the full compliance with national and international standards and ethical and legal values.

The main goal of the National Administration in managing its procedures is the fulfillment of efficiency, economy, transparency and predictability principles.

The experience gained in the systematic application of the abovementioned Provision requires reviewing and updating procedural aspects in order to update and speed up the assessment of authorizations to perform clinical studies.

In particular, section 2 of ANMAT Provision No. 6677/10 sets forth the term established for the ANMAT to issue a resolution regarding the documentation referred to in the regime approved by this Provision and states that such term may be suspended if objections are made and until the interested party submits all the documentation and/or complies with all requested observations and/or clarifications.

Such section should be amended to set the term for the issuance of the technical reports and the administrative act, as well as the conditions required for the terms to be resumed if suspended as a result of objections made by the technical areas involved.

The amendment of the term to apply for clinical pharmacology studies under the competence of this National Administration gives rise to the obligation to establish conditions in order to meet the specific requirements in filing those procedures.

It is required to ensure the proper implementation of Phase I clinical pharmacology studies through the highest ethical and scientific standards, reducing potential risks for the volunteers participating in those studies.

An efficiency and predictability framework should be provided to develop Phase I clinical pharmacology research studies, as a complement of general requirements under ANMAT Provision No. 6677/10.

The National Drug Institute, the Drug Evaluation and Registration Office and the General Department of Legal Affairs have become involved within their competence.

Actions are taken pursuant to the powers granted by Decree No. 1490 dated August 20, 1992, and Decree No. 101 dated December 16, 2015.

Therefore,

THE NATIONAL ADMINISTRATOR OF THE NATIONAL ADMINISTRATION OF FOOD, DRUGS AND MEDICAL TECHNOLOGY RESOLVES AS FOLLOWS:

SECTION 1. Section 2 of ANMAT Provision No. 6677/10 is replaced to read as follows “Section 2. Once the documentation referred to in the regime approved by section 1 of this Provision is filed and accepted, the technical areas involved shall issue a provision within 60 (sixty) administrative business days. Such term may be suspended if objections are made and until the interested party submits all the documentation and/or complies with all observations and/or requested clarifications. Once the report is issued, the relevant administrative act shall be issued within 10 (ten) administrative business days.”

SECTION 2. The DERM (Direction of Drug Evaluation and Registration) shall verify whether the documentation complies with the requirements under ANMAT Provision No. 6677/10 and this Provision. Within 3 (three) administrative business days from the date following that on which the DERM receives the files, the DERM shall duly notify the sponsor whether the request is ready to be evaluated and, in that case, the term under sections 1 or 3 hereof shall begin. If the sponsor does not submit all the required documentation, the application for authorization of the clinical trial shall be denied without further formalities.

SECTION 3. If the sponsor chooses to apply for the authorization of a clinical pharmacology study falling into any of the following circumstances: a) approved by health authorities from any of the countries under Annex I, Decree No. 150/92 (as amended in 1993), and in progress in at least one of those countries; b) approved and in progress in countries deemed to be consistent by the ANMAT in due time with its regulations and as from such consideration; or c) approved and in progress in countries recognized by the Pan American Health Organization/World Health Organization (PAHO/WHO) as reference national regulatory agency; the terms set in section 1 hereof shall be 45 (forty-five) administrative business days for the issuance of the final technical report by the technical areas involved, and 10 (ten) administrative business days for the issuance of the relevant administrative act.

SECTION 4. The approval and conduction of the study shall be evidenced as indicated in the previous section by filing the following documentation translated by a registered translator:

1) Proof of IND (Investigational New Drug) request issued by the U.S. Food and Drug Administration (FDA), or proof of EUDRACT (European Clinical Trials Database) submission and number, or proof of approval issued by other countries included in Annex I, Decree No. 150/92 (as amended in 1993), or

2) Proof of approval by agencies of the countries indicated in items b) and c), section 3, or

3) Sponsor's sworn statement showing that the study has been implemented in a country included in Annex I, Decree No. 150/92 (as amended in 1993) and/or in one of the countries indicated in items b) and c), section 3.

SECTION 5. Item 2.2 "Request for authorization of investigator and research site" under "SECTION B: REQUIRED DOCUMENTATION TO APPLY FOR THE AUTHORIZATION OF CLINICAL PHARMACOLOGY STUDIES, item 2. GENERAL DOCUMENTATION" of the Annex under ANMAT Provision No. 6677/10 is replaced to read as follows:

2.2. Request for authorization of investigator and research site: to obtain the authorization of each principal investigator and research site, the sponsor shall submit:

2.2.1. In jurisdictions having a central accreditation body (e.g. Central Ethics Committee) accrediting the Research Ethics Committees (RECs) operating within the area of that jurisdiction:

a) Information on the investigator, the research site and the REC:

Name of investigator

Name of site

Site address

Telephone/fax

Email

Name of REC

REC address

b) Within 30 days from the acceptance of the documentation to evaluate the clinical pharmacology study, the sponsor shall submit an authenticated copy of the REC's resolution approving the investigator to conduct the protocol of the clinical research at the research site.

2.2.2. In the remaining jurisdictions:

(a) complete and signed form EFCA2 (Section F);

(b) summarized curriculum vitae signed and dated by the investigator;

(c) authenticated copies of the professional degree and professional registration at the health jurisdiction where the study is conducted, and proof of training and/or experience in clinical research;

(d) for Phase II and III studies, an authenticated copy of the specialist degree, full internship certificate or postgraduate certificate showing specialization in the study disease;

(e) original note of the commitment to comply with the study protocol (indicating the title), the Declaration of Helsinki and ANMAT's Good Clinical Practice Regime for Clinical Pharmacology Studies;

(f) authenticated copy of the study approval by a research ethics committee (REC), specifying all reviewed documentation, such as protocol, informed consent and monograph of the research product. Only one REC approval shall be accepted per each research site;

(g) dated listing of the members of each REC, including name, date of birth, gender, profession or occupation, position in the committee and relationship with the institution;

(h) authenticated copy of the study authorization by the highest authority of the institution where the study is conducted;

(i) authenticated copy of the authorization granted by the authority of the institution where the study will be conducted for study review by an external REC, as applicable;

(j) authenticated evidence of the sanitary license effective at the research site;

(k) customized informed consent for the site, as applicable.

SECTION 6. If, during the evaluation process, the sponsor submits any amendment to the protocol or a new product monograph, the terms set in sections 1 or 3 hereof shall be suspended, as applicable.

SECTION 7. If the terms set in this Provision elapse and no report has been issued by the competent areas, the sponsor may commence the clinical pharmacology study whose approval had been requested and, as a previous requirement, it shall request the ANMAT through reliable means to issue the relevant technical report within 5 (five) administrative business days and, if favorable, that an administrative act be issued to approve conduction of the study.

SECTION 8. Upon verification that the documentation submitted by the sponsor is inaccurate and/or does not comply with the regime established by ANMAT Provision No. 6677/10, this National Administration may deny the request for approval of the clinical pharmacology study.

SECTION 9. If ANMAT notifies any grounded objections, the term set in sections 1 or 3 hereof shall be interrupted. The sponsor shall have 15 (fifteen) administrative business days to amend its request in view of the objections raised or, in the event of a discrepancy with those objections, provide reasons and the documentation that it may deem relevant to support its request.

If the term established in the previous paragraph elapses without the requesting party amending the request or providing arguments, the request shall be denied without further formalities.

SECTION 10. This Provision shall be applied to all clinical pharmacology study protocols evaluation requests submitted as from its effective date.

SECTION 11. SPECIFIC CONSIDERATIONS ON PHASE I CLINICAL PHARMACOLOGY STUDIES

11.1. PROTOCOL

Phase I protocols shall be mainly aimed at providing a research plan —estimating the number of patients to be included, describing safety exclusions, describing the dosage plan, including duration, dose or methods to determine the dose— and they shall specify in detail only the study elements that are critical for safety, such as the required monitoring of vital signs and blood chemistry.

In particular, the protocol should:

- Clearly describe the criteria for dose increase and for volunteer withdrawal.

- Describe the methods to evaluate and control safety during the study.

- Describe the risk assessment analysis and contingency plans.

11.2. RESEARCH SITES

11.2.1 General considerations

First-time-in-human studies using medicinal products with high potential risks on human beings shall be conducted at appropriate clinical facilities. Phase I pharmacokinetics, bioavailability and bioequivalence studies shall be conducted only at duly registered, supervised and categorized healthcare facilities registered with the Federal Registry of Health Establishments (REFES, for its Spanish acronym), in accordance with Ministry of Health Resolution No. 1070/09, by medical staff having an appropriate level of training and experience and knowledge of the research medicinal product, its target organ and mechanism of action.

Immediate access must be granted to facilities for medical emergency treatment (e.g. cardiac emergencies, anaphylaxis, cytokine release syndrome, seizures, hypotension), facilities to stabilize individuals in the event of an acute emergency, and immediate availability of facilities for intensive care units.

11.2.2 Specific requirements

- Emergency equipment and procedures.

Emergency equipment and medication availability and maintenance.

Crash cart whose content and equipment have been validated by a physician specialized in intensive care.

Medical supervision (with support staff during the night, as required) for 24 hours following the dosing of the investigational drug.

Possibility for monitoring hospitalized patients (central control area or video surveillance system.)

Proper area for study drug maintenance and preparation (temperature and control conditions.)

Electric power supplementary source.

Volunteer recreation area.

Food supply.

Controls over the entry of staff with limited or unauthorized entry.

- Standard Operating Procedures (SOPs).

They must cover all protocol essential procedures and, in particular:

Measures to ensure volunteers' compliance with the protocol

Subject monitoring

Subject identification during their stay

Medical record documentation

Food documentation

Procedures upon emergencies

Site staff training for emergency equipment management

11.3. - SITE INVESTIGATOR AND STAFF

The investigator must:

- Have due knowledge of the investigational drug pharmacology.

- Ensure the presence of specialized medical staff with an appropriate level of experience and training.

- Ensure the presence of appropriate and sufficient site staff during the 24 hours following the dosing of the investigational drug.

- Ensure the training of site staff for emergency equipment management.

11.4 APPROVAL AND AUTHORIZATIONS

12.4.1 Sites

Once all applicable requirements under Provision No. 6677/10 and this Provision have been met and documented, a site conducting Phase I clinical pharmacology research studies shall request ANMAT's authorization and, for that purpose, the site will be inspected. Depending on the outcome of the inspection final report, the ANMAT shall grant the authorization to conduct Phase I clinical pharmacology research studies, for an effective term of 5 years.

This authorization shall expire if the site fails to conduct a clinical pharmacology research study for two years following the date on which it was granted. To renew the authorization, the site shall request a new inspection from the ANMAT.

Apart from the authorization procedure described in this section, the site may be inspected during or after study conduction, in accordance with the provisions under ANMAT Provision No. 6677/10.

11.4.2 Studies

Phase I clinical pharmacology research studies may be conducted only in sites holding an effective authorization from the ANMAT and, for that purpose, relevant documentation shall be submitted as part of the study approval request.

The sponsor shall file a meeting request by virtue of ANMAT Circular No. 001/13, pursuant to current regulations, which shall be granted in no more than 15 (fifteen) administrative business days.

The committee created by virtue of ANMAT Circular No. 001/13 shall be formed by representatives of the areas that will be subsequently in charge of issuing the technical report. The minutes drafted for that purpose shall contain the findings and/or request for clarifications made during the meeting.

The sponsor shall submit the study approval request, along with the relevant documentation required by ANMAT Provision No. 6677/10 and this Provision, as well as the ANMAT Circular No. 001/13 minutes and the responses to the findings and/or request for clarifications, as applicable.

Within 20 (twenty) administrative business days, the areas involved shall prepare the final technical report and an additional term of 10 (ten) administrative business days shall be available for the issuance of the administrative act approving or denying the request.

SECTION 12. This Provision shall become effective 30 (thirty) calendar days as from the date following its publication in the Argentine Official Bulletin.

SECTION 13. Provisional Provision: Within the term of 30 (thirty) days set in the previous section, the Information Technology Department shall make the amendments required to the processing regime regarding the request for authorization of a clinical pharmacology study and it shall adapt the relevant instructions.

SECTION 14. Be it registered. Be it delivered to the Direction of the Official Registry for publication purposes. Be it notified to the Industrial Chamber of Argentine Pharmacists (CILFA), the Argentine Chamber of Medicinal Specialties (CAEMe), the Business Chamber of Pharmaceutical Laboratories (COOPERALA), the Argentine Chamber of Clinical Research Organizations (CAOIC), the Argentine Chamber of Producers of Generic Medicines and Drugs for Hospital Use (CAPGEN), and the Argentine Chamber of Over-the-Counter Medicines (CAPEMVeL). Be it notified to the National Drug Institute, the Information

Technology Department and the Planning and Institutional Relations Department. Once fulfilled, be it filed. - Carlos Chiale.

e. 04/05/2017 No. 29075/17 through 04/05/2017