The purpose of this presentation is:

- To provide a general presentation of documents needed and scope of work by ANMAT.
- To highlight requirements in addition to GCP (ICH E6 Guideline).
- To highlight changes from previous ANMAM regulatory requirements regarding clinical pharmacology research studies and ANMAT Inspections to Clinical Investigators.
ANATOMY OF
6677/2010 ANMAT Provision

Section A - General Terms
Section B - Documentation Requirements for Authorization Request of Clinical Pharmacology Studies
Section C - Good Clinical Practice for Clinical Pharmacology Studies
Section D - Clinical Pharmacology Study Inspections
Section E - Glossary
Section F - Forms
6677/2010: CHANGE OF SCOPE

Provision shall apply only to:

- Pharmacology studies (Phase I, II and III)
- Studies with products which are registered with ANMAT only if they involve:
  - new indication,
  - increase in the already registered concentration,
  - new posology or
  - new pharmaceutical from with registration purposes.

- All Pharmacokinetics, bioavailability and bioequivalence studies.
Requirement Updates (B2)

- Safety Reports (SUSARS) presented each 6 months
- The following deviations are to be reported within 10 working days since awareness by Sponsor/CRO:
  - Those affecting rights or safety of subjects, or – those that are minor but repeated in spite of Investigator warning of recurrence
- Annual and Final periodic reports by Investigator and Sponsor/CRO since Authorization by ANMAT and will include report of changes in
  - Monitoring Plan - Research Ethics Committee Composition - Sponsor/CRO or Investigator contact details
Requirement Updates (B2)

Documents not required to be presented in the CTA, but will be requested in case of site inspection:
- Case Report Form Samples
- Subject Diary, QOL questionnaires
- Material to be used for explanation of study to potential participants
- Monitoring Plan
Forms to be submitted to ANMAT during the course of a Study as per 6677-2010:

- Sponsor/CRO Study Authorization Request Form (EFCA 1)
- Site/Investigator Activation Form (EFCA 2)
- Sponsor/CRO Study Amendment Authorization Request Form (EFCA 3)
Forms to be submitted to ANMAT during the course of a Study as per 6677-2010:

- Investigator Drug Brochure pdate Presentation: EFCA 4
- Sponsor/ CRO periodic/ final report to ANMAT: EFCA 5.1
- Investigator periodic/ final report to ANMAT: EFCA 5.2
Regulatory Flowchart

Process: 5 – 6 Months

Local Ethic Committees

- Protocol + ICF + IB
  - Submission: 2 weeks
  - Approval: 4 weeks

ICF

- MoJ (DNPDP) Submission
  - 3 days
  - MoJ (DNPDP) Approval: 1 week

Import License

- Drug at Depot: 1 week

MoH Approval + Import license

- MoH (ANMAT) Submission: 12 weeks
Investigator (C2)

- Investigator and his/her co workers must verify and guarantee sanitary permits of the site, adequate infrastructure for study requirements and adequate equipments, instruments and materials to be used. *Phase I, pharmacokinetics and bioequivalence studies can only be conducted in 2nd or 3rd level health institutions according to Ministry of Health regulations and sanitary permits.*

- If Investigator uses media to communicate clinical studies in order to recruit participants, the study specific material must be approved by the Research Ethics Committee and presented to ANMAT. *Message will not imply or explicitly state that investigational product efficacy or safe or better than other existing products.*
Sponsor (C3)

- If sponsor is a foreign company and delegates in a CRO clinical study conduct and in the country management, designated CRO will be subject to compliance with this regulation as in the role of study sponsor assuming all administrative, civil and compliance responsibilities.

- Incompliance with protocol on behalf of investigator or sponsor representative will lead to an immediate corrective action on behalf of sponsor.

- If sponsor identifies protocol incompliance that is also repeated, persistent or serious on behalf of investigator, study must be suspended and both Research Ethics Committee and ANMAT must be informed.
Ethics Research Committee (C4)

- Must be affiliated to an Institution and if site does not have one it can surrogate on one affiliated to an Institution.

- Must request immediate communication of all relevant safety information or protocol changes that may pose risk increase to subjects or changes meant to decrease risk to study participants.

- Any study related information that does not pose risk can be assessed in an expedited way by a member who must document the decision and inform all other members.

- Records must be kept with all study related documentation including reviewed documents, meeting minutes, documented opinion of all reviews and general communications. Must be kept for 10 years after study finalized and be available to ANMAT if required.
Informed Consent (C5)

In case of educational vulnerability of the potential subject, whether cultural, social or economic; a witness who must be independent from the Investigator must participate, signing and dating the ICF form as proof of process participation. In sites where this population prevails, Research Ethics Committee (REC) may decide that this will be a requirement for obtaining all Informed Consents.

In acute setting that require an immediate medical Intervention, a summary of the written information to the study participant may be used, if previously approved by REC and ANMAT. Oral information must be given in presence of an independent witness who will sign, together with the investigator, and the subject the written summary of the given information.

• 29 elements as detailed in B.5.1 must be contained in the Informed Consent Form
Participant Protection (C6)

Pregnancy Risks during Clinical Research Participation •

- Pregnancy test must be performed in all women with bearing potential before starting participation and regularly during the study.

- Positive pregnancy result will imply that potential participant must not be included or participation in study will be suspended preventively as applicable. In this case, Investigator will counsel patient to receive proper medical care and attention.

- Investigator and sponsor must guarantee study participants access to contraceptive methods.
Agreements and Financing (C7)

- Sponsor is responsible for covering all research costs, including protocol treatment and study procedure.

- Sponsor must provide medical coverage and insurance or another assurance in the country in case of injury associated to study participation.

- Investigator must disclose potential conflict of interest with Research Ethics Committee before study begins and at any time after should they occur.
Investigational Product (C8)

- If expiration date should need updating, new label to be attached to the bottle must include:
  - Lot number
  - Previous re test or expiration date
  - New expiration date

- If re-labelling is done at investigational site, study CRA and a second sponsor representative should be present, and process must be documented and supporting documentation provided to site.

- Sponsor is responsible for destroying unused investigational products and must retain the certificate of the destruction process, which must be in compliance with local regulation on destruction of dangerous goods.
Communications (C9)

- Sponsor must communicate all SUSAR in 14 days since sponsor awareness and Investigators must report RAMSI to Research Ethics Committees as requested by their own SOPs.

- Sponsor must inform ANMAT all SUSAR and other safety information related to the investigational product within 10 days of awareness.
Clinical Data Recording (C11)

The following information must be registered in the same format as other medical records used for patients that attend the clinical site on a routine basis:

- ICF process
- Screening assessment
- Inclusion in clinical study
- Randomization process Instructions for Investigational product administration
- Start and end of study treatment
- Dispensing and return of study treatment Information to study participant
Clinical Data Recording (C11)

If electronic records are used for registration and reporting of clinical data used the system must allow:

- Registration of all editions of individual data, including author and date of edition, and without eliminating original data,
- restricted permission to access or edit data,
- built in Back up of Data, and
- protection of blinding information during registration and processing of data, as applicable.
Monitoring (C13) and Auditing (C14)

Monitor Must ensure that:

- all Research Ethics Board and Competent Authorities approval have been obtained,
- the recruitment rate of the study is appropriate, and
- source document, CRF and product inventory are precise, complete, legible, coherent and in time, whereas subject confidentiality is preserved in all of these records.

Sponsor must implement an audit process as part of the Quality Assurance system.

- All Audit Findings must be reported to sponsor and audit procedures must be in compliance with sponsor SOPs
- Audit Reports must be communicated to ANMAT if required or if they show evidence of serious incompliance or if a legal procedure is in course.
之称 Inspections of clinical studies are mainly destined to Investigators and clinical research sites. However ANMAT may determine the need to inspect other instances involved in the activity such as sponsor or CRO.

- ANMAT inspectors are enabled to access the clinical research site and access directly the investigational product, participant clinical study records and any other study documentation. Inspection of clinical research studies may include external institutions that are involved in study specific procedures and processes. Such institutions may be contracted either by Investigator, sponsor or CRO.
## ANMAT Inspections (D)

### Selection of Study and Investigator (D4)

- Studies that include vulnerable population.
- Studies of Phase I-II Clinical Research.
- Studies on investigational products of associated high risk.
- Investigators that show a high recruitment rate in relation to other investigators in the same study. High or low SUSAR risk in relation to other Investigators in the same study.
- Investigator is participating in a significant number of studies.
- Any relevant information received in safety reports or periodic reports that justifies an Investigator Inspection according to ANMAT criteria.
- Reports received by ANMAT related to inappropriate conduct by Investigator.
ANMAT Inspections (D)
Inspection Communication (D7)

- Inspections will be previously informed to Sponsor and/or Principal Investigator with at least 15 calendar days previous to the designated date, in order to guarantee availability of research staff at the time of inspection.

- If the inspection is prompted by safety reports, periodic progress reports or a report due to inappropriate conduct by Investigator, previous announcement of inspector visit may not apply.
ANMAT Inspections (D)
Initial Interview (D 8.2)

- Inspections will show official identification, explain scope and audit procedures.

- During the Initial Interview Investigator study Staff and sponsor representatives are allowed to be present.

- Inspectors will request information who, what, when, where and how about the delegation of functions to Investigator staff related to several items including potential study participant evaluation and selecting and randomizing study participants.

- Inspectors may conduct interviews during the initiation to Investigator study staff and if relevant to study participants.
ANMAT Inspections (D)

Inspection Progress (D 8.3)

- Inspectors may interview study participants and such interviews will be documented in separate records from those of the Inspection procedure. Such records will contain:
  - Participant ID
  - Interview objective or purpose
  - Questions that are expected to be answered
  - Answers received from study participants in the interview process

To be filed with ANMAT and will only be accessed by Investigator if the request is justified and ANMAT expressly authorizes to do so.

- If during the Inspection serious deviations to the regulation or serious risk to study participants are identified, inspectors may decide to interrupt study continuity.
Inspected will review essential documents of investigator as per section C of this regulation.

Review of Informed consent documentation will include:
- If informed consent has been obtained from a legal representative of the study participant, such power of representation will be documented with the clinical records.
- The informed consent process is documented in the clinical records of the participant including:
  - date and time of process initiation,
  - clarification whether ample time was given to potential subject to reflect and ask questions,
  - which where the questions the potential subject asked,
  - that understanding of the information given was verified and
  - that two originals were signed and one given to the study participant.

In the case of cultural, educational or economically vulnerable subject, informed consent has been obtained in the presence of an independent witness who has also signed and such process is documented in detail.
ANMAT Inspections (D)

Documentation Review Continued (D 9)

- If Inspectors identify major deviation in any study procedure, such study procedure will be reviewed in a bigger sample of subjects than the one originally planned.

- Inspectors will verify gratuity of products and study procedures and any protocol related payments to subjects by proof of purchase or documented receipt or invoicing to Investigator or sponsor in the case of study related tests or exams
ANMAT Inspections (D)

Inspection on Site Records (D 10)

- If Inspectors will write an inspection on site report detailing the **type** of revision and scope of review done during the inspection, as well as observations, findings and problems identified.

- If observations or issues remain to be answered or clarified, the inspected party will have 10 working days to provide such answers and clarifications.

- Inspection on site records will be signed in three original parts by investigator/sub-investigator, Inspectors and sponsor representative; such originals will be distributed one for each party accordingly.
Further action is needed on behalf of ANMAT

**Preventive actions may include:** temporary suspension of recruitment, temporary suspension of study at inspected site, restriction to investigator from conducting new studies.

**Definite measures may include:** definite suspension of recruitment of subjects, definite suspension of inspected study, definite suspension of all studies at inspected site, suspension of inspected study at all sites involved in the country, request to sponsor to intensify study monitoring, request to sponsor to change investigator at site, request to sponsor to discard study data generated at the site, notification to medical school where Investigator is affiliated, administrative or legal action towards investigator and / or CRO and/ or sponsor.
THANK YOU!!!

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