University
Joints
Industry
14th March 2018

Clinical and Drug Safety

Galenicum believe in life

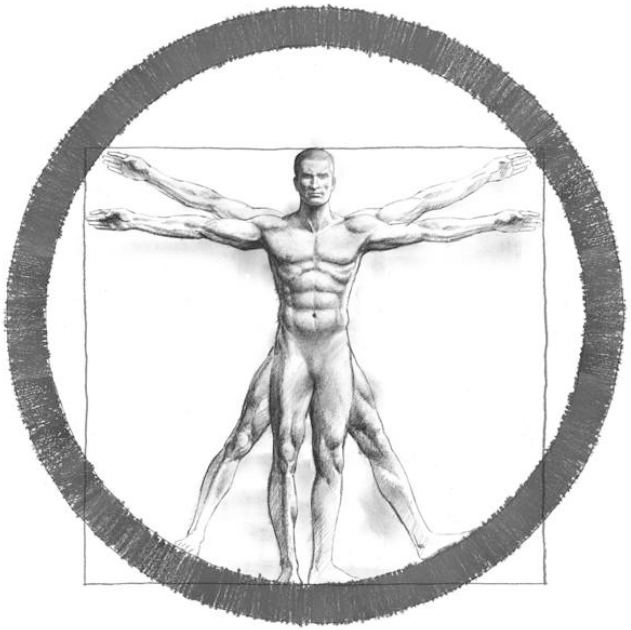
Presentation

Marta **Forcadell** Ferré

- Graduated in **Biochemistry** by the University of Barcelona
- Post–graduated in **Scientific Departments of the Pharmaceutical Industry** by ESAME
- Specialised mainly in Clinical Trials (Bioequivalence studies) and Pharmacovigilance
- Professional Experience in Galenicum since one year ago

Clinical Department in Galenicum

- Mainly graduated in **Pharmacy**
- Post–graduated in a **Pharmaceutical Industry related Master**
- Specialised mainly in Regulatory Affairs, Clinical Trials (Bioequivalence studies) and Pharmacovigilance

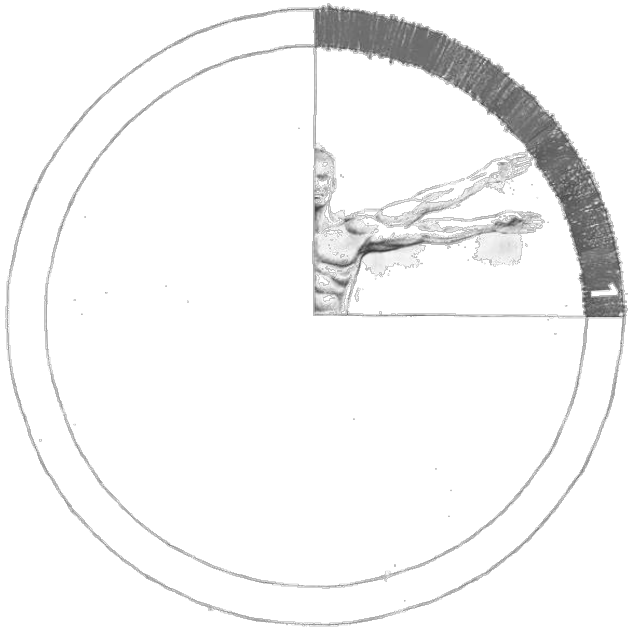


Clinical trials

Generic-Bioequivalence Studies

Pharmacovigilance

Career/Development skills



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Introduction to Clinical Trials

For the purposes of registration, a clinical trial is any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.

The regulation of clinical trials aims to ensure that the rights, safety and well-being of trial subjects are protected and the results of clinical trials are credible.

ETHICS:

Nuremberg Code (1947)

Declaration of Helsinki (1964) is a set of ethical principles regarding human experimentation developed for the medical community by the World Medical Association.

Belmont Report (1978)

- Core principles:
  - ✓ Respect of persons
  - ✓ Beneficence
  - ✓ Justice
- Areas of application
  - ✓ Informed Consent
  - ✓ Assessment of risks and benefits
  - ✓ Selection of subjects

"Half the diabetics were given the new drug and responded well. The other half got a placebo and went into shock."

LEGISLATION:

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, recording and reporting trials that involve the participation of human subjects.

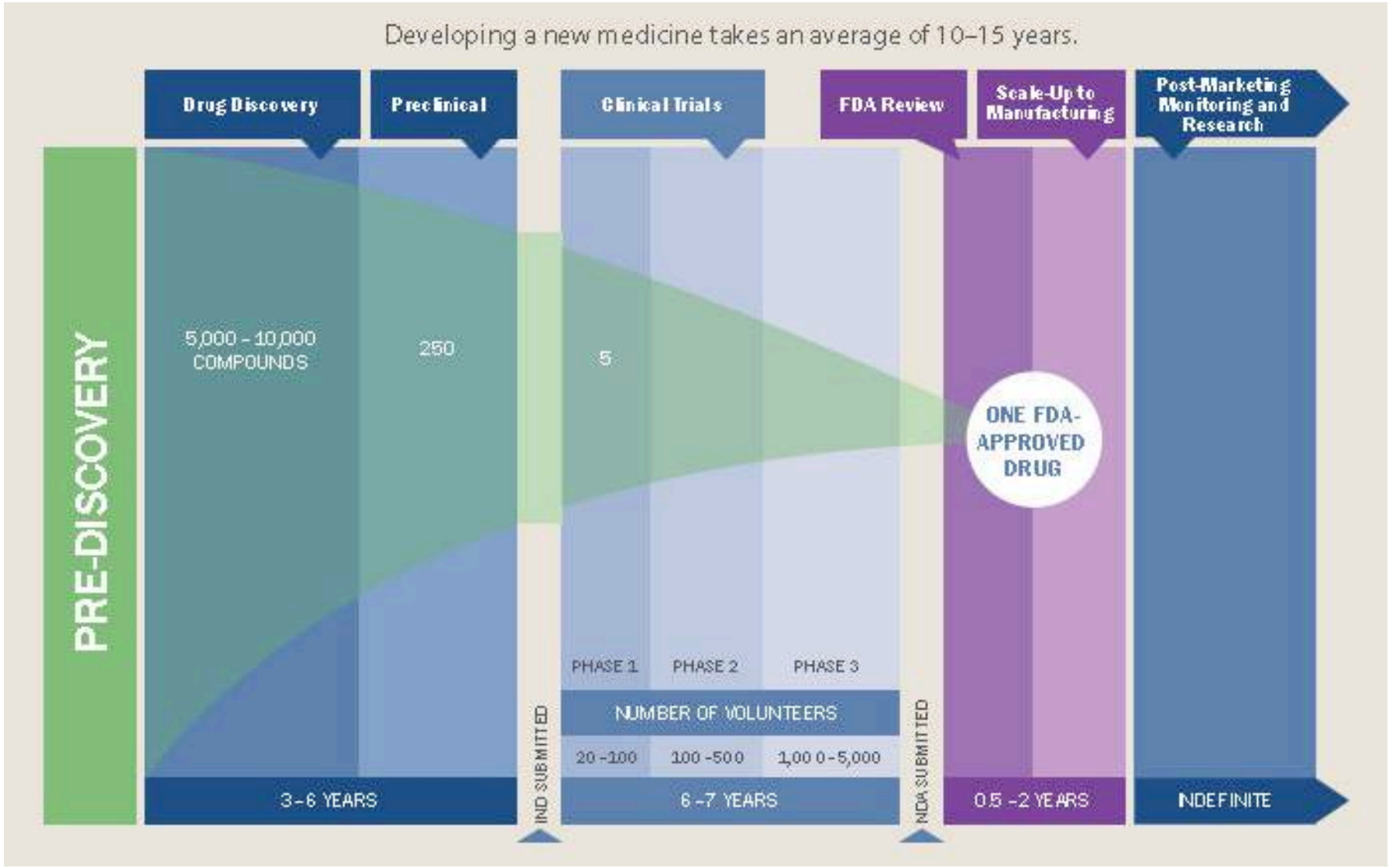
International Conference Harmonisation (ICH)

Directive 2001/20/EC

Regulation EU NO 536/2014

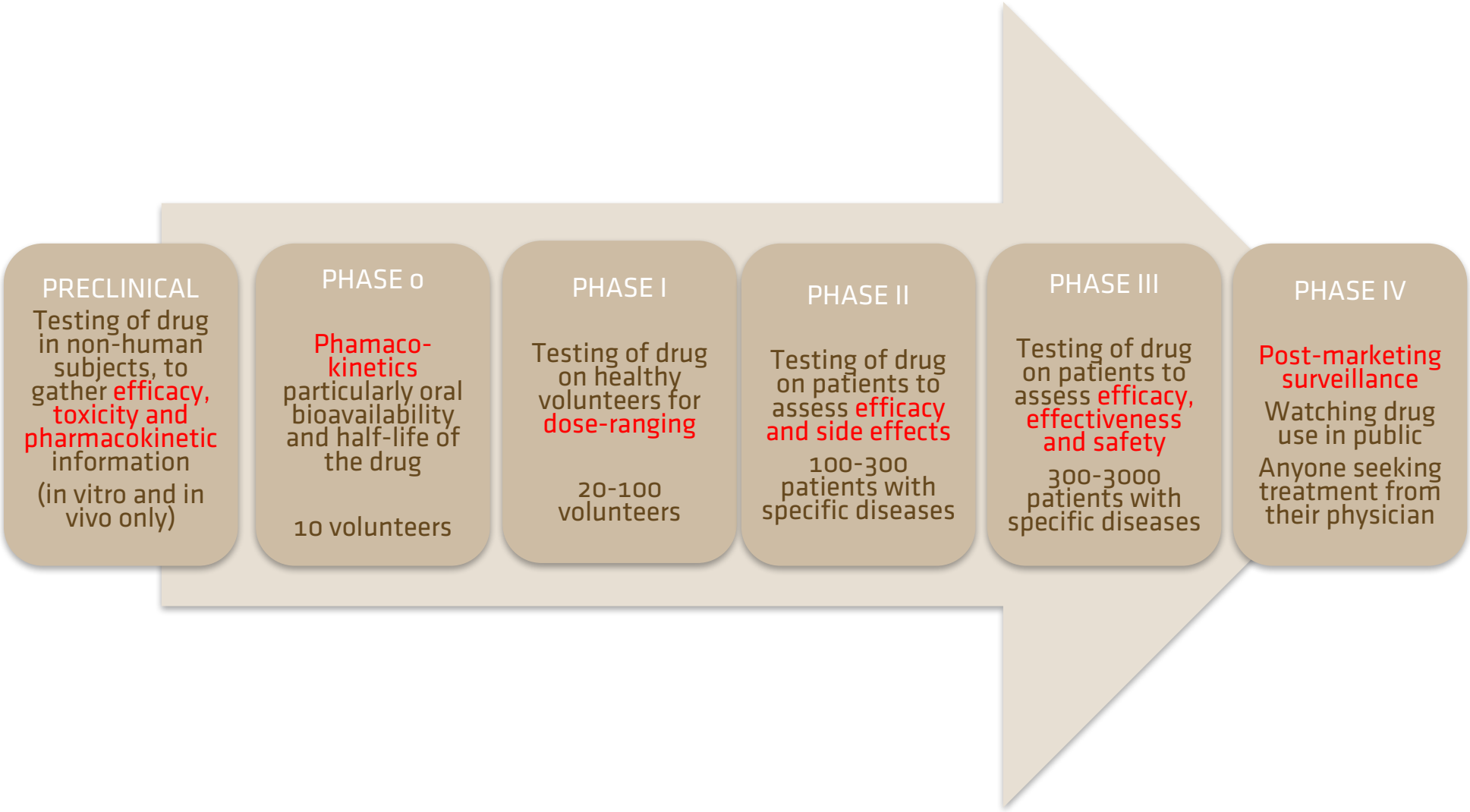
Real Decreto 1090/2015

The Research and Development Process

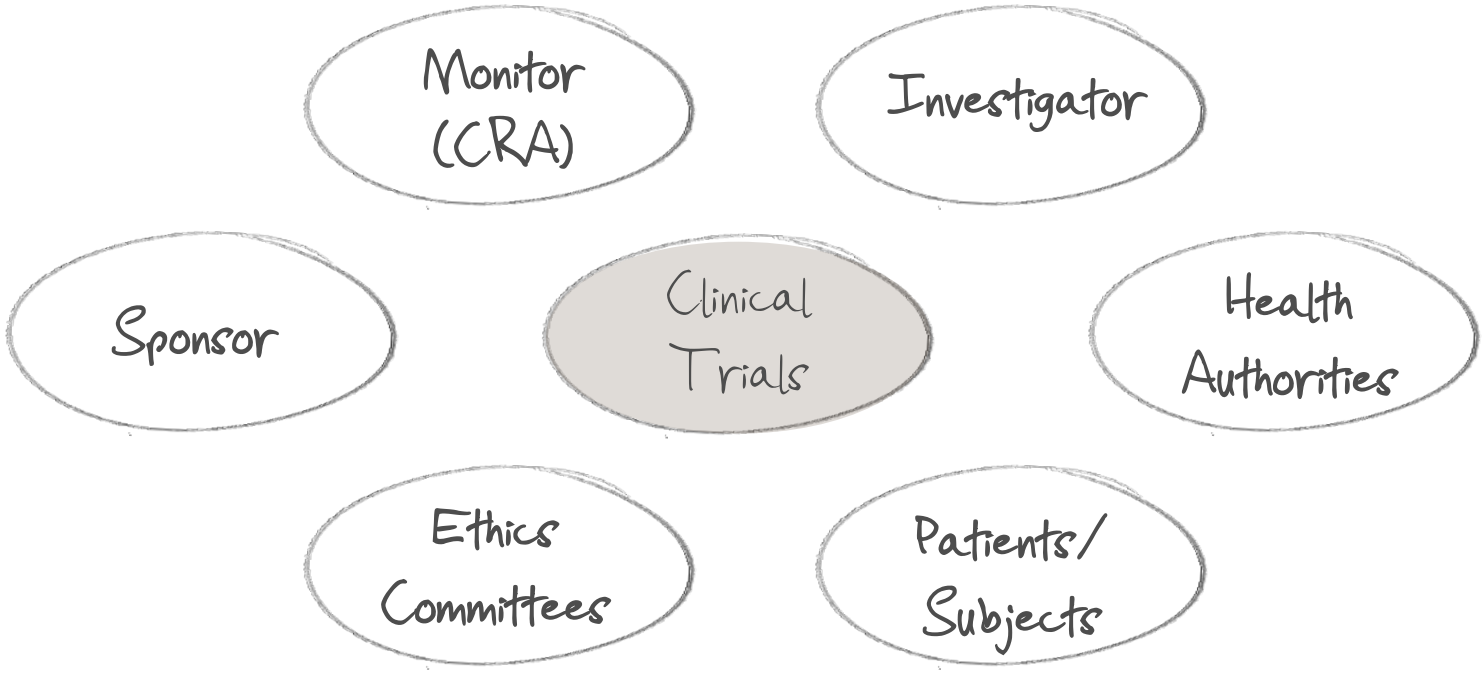


SOURCE: Pharmaceutical Research and Manufacturers of America, Drug Discovery and Development (www.innovation.org)

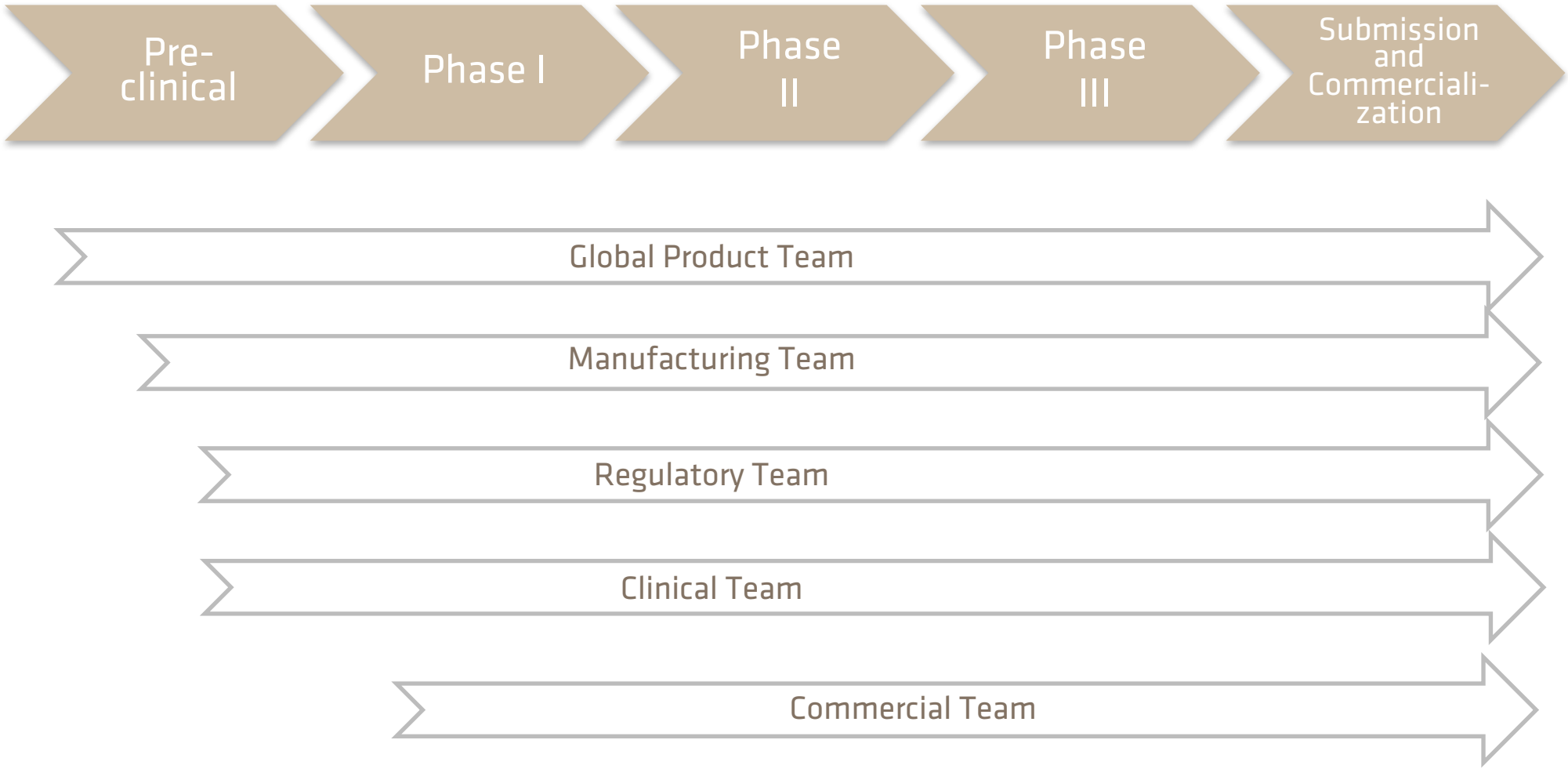
Summary of Clinical Trial Phases

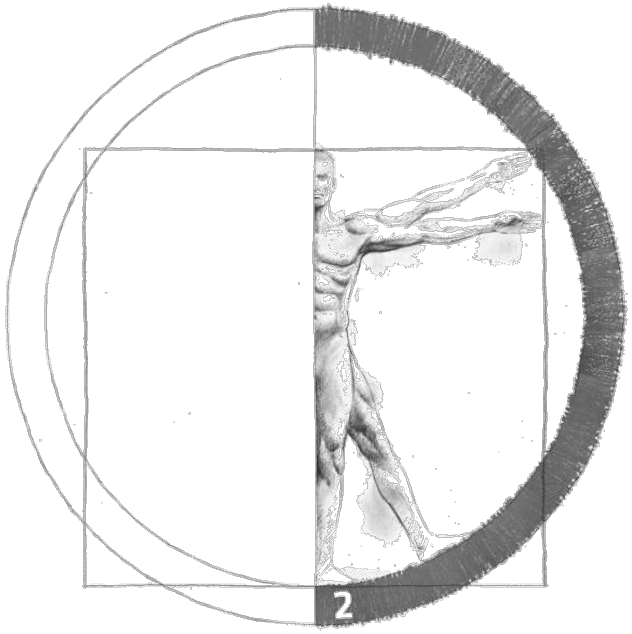


Stakeholders in Clinical Trials



Stakeholders in Clinical Trials





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GENERIC Definition

Ley Garantías 29/2006 Dir. 2001/83/EC (1990 Ley del Medicamento)

- La misma composición cualitativa y cuantitativa en principios activos
- La misma forma farmacéutica
- Bioequivalencia con el medicamento de referencia

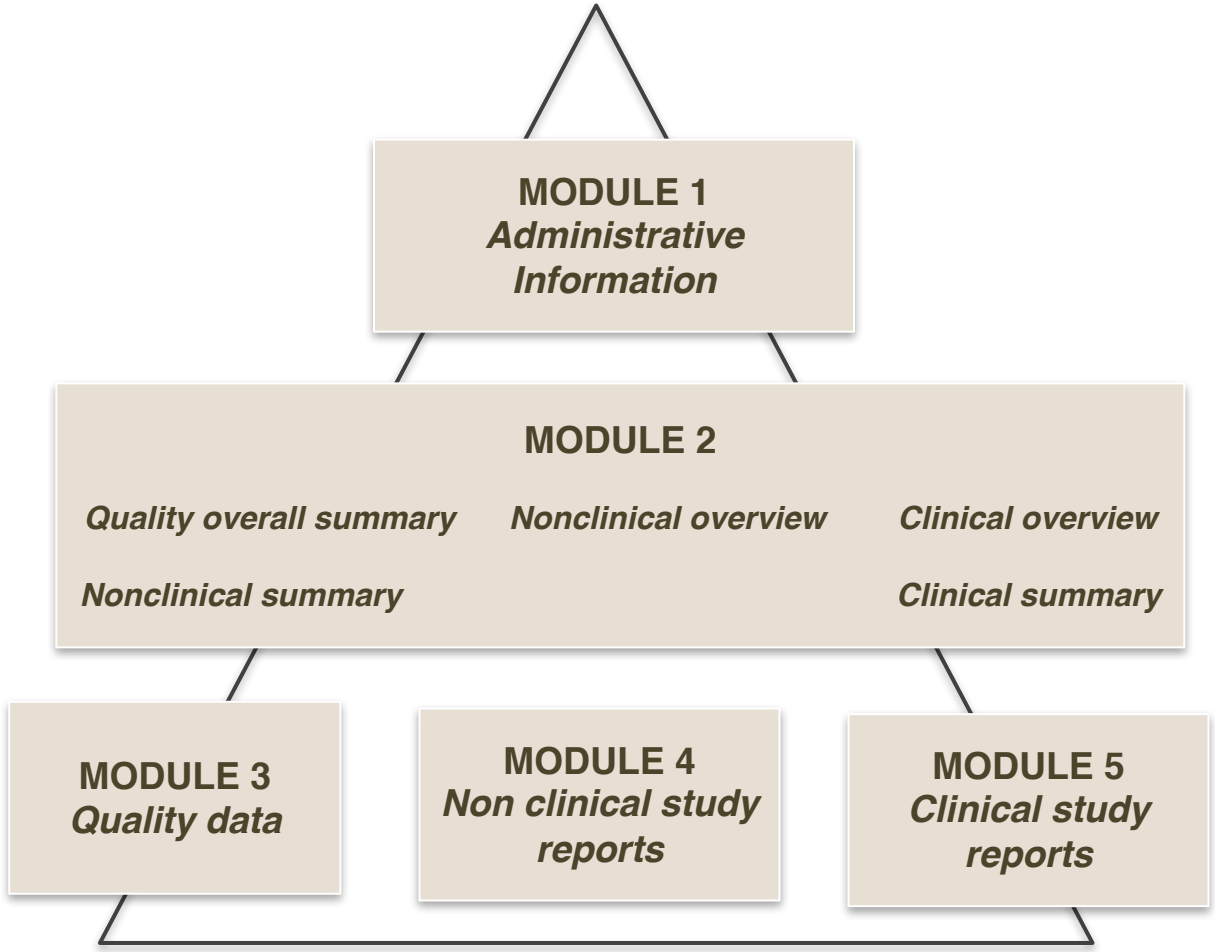
Diferencias con los productos de referencia:

✓ Excipientes (condicionan la prescripción en casos muy concretos)
✓ Apariencia (color, tamaño, forma, sabor, embalaje)
✓ Laboratorio fabricante (puede ser el mismo)

Registration Dossier: Common Technical Document (CTD) format)

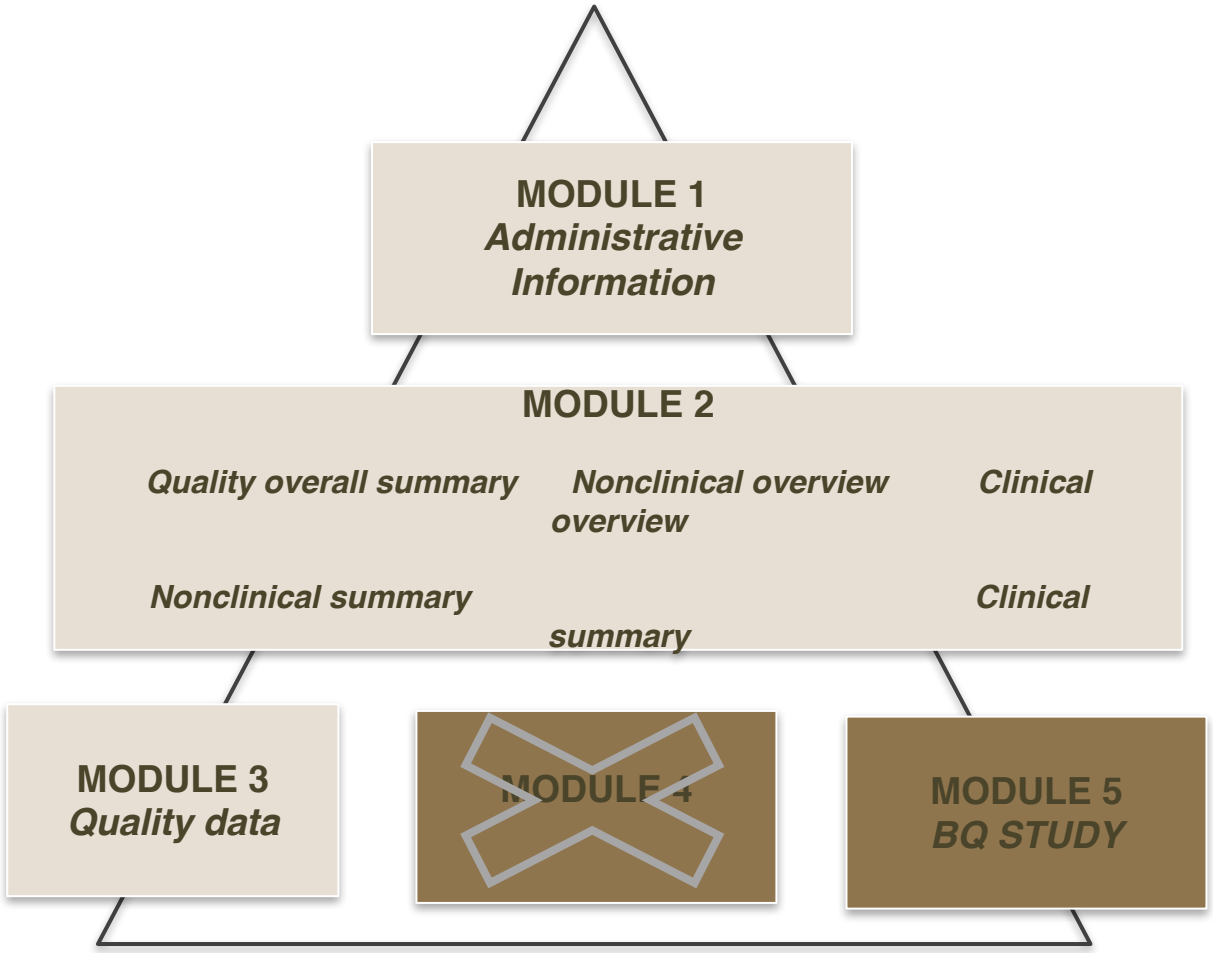
TYPE OF DOSSIERS:

1. **COMPLETE/STAND-ALONE: Innovator (Art 8.3) or Bibliographical (Art. 10a)**



TYPE OF DOSSIERS:

2. ABRIDGED: linked to one already approved, ex. GENERIC



GENERIC PRODUCT: Bioequivalence

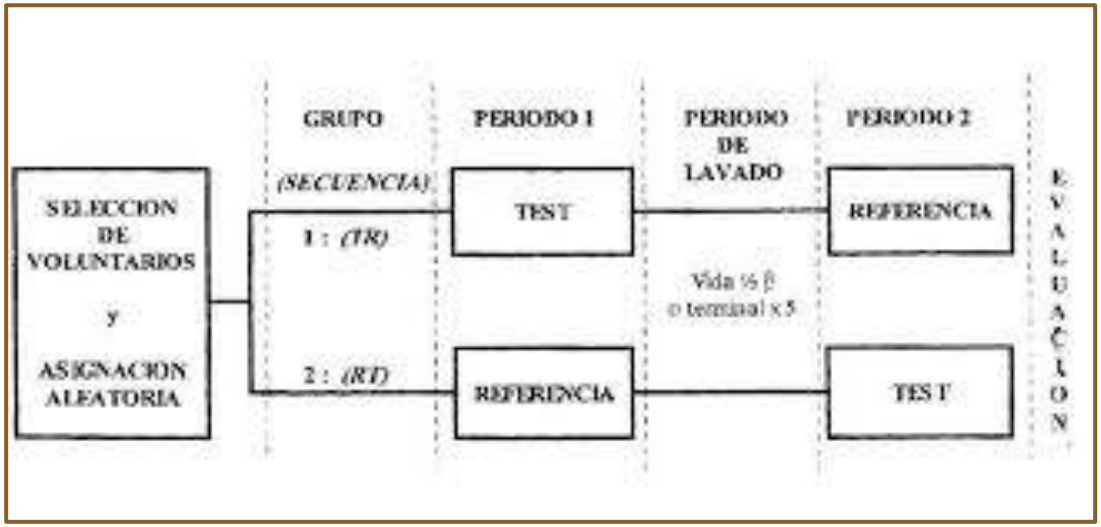
BIOEQUIVALENCE based on CPMP/EWP/QWP/1401/98, Jan 2010:

Two medicinal products containing the same active substance are considered bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavailabilities (rate and extent) after administration in the same molar dose lie within acceptable predefined limits. These limits are set to ensure comparable in vivo performance, i.e. similarity in terms of safety and efficacy.

Bioequivalence studies

Design of the study

- Clinical trials Phase I:
  - Pilot study
  - **Pivotal study**
  - Simple o replicative
- Principal parameters:
  - Cmax
  - AUC
  - tmax

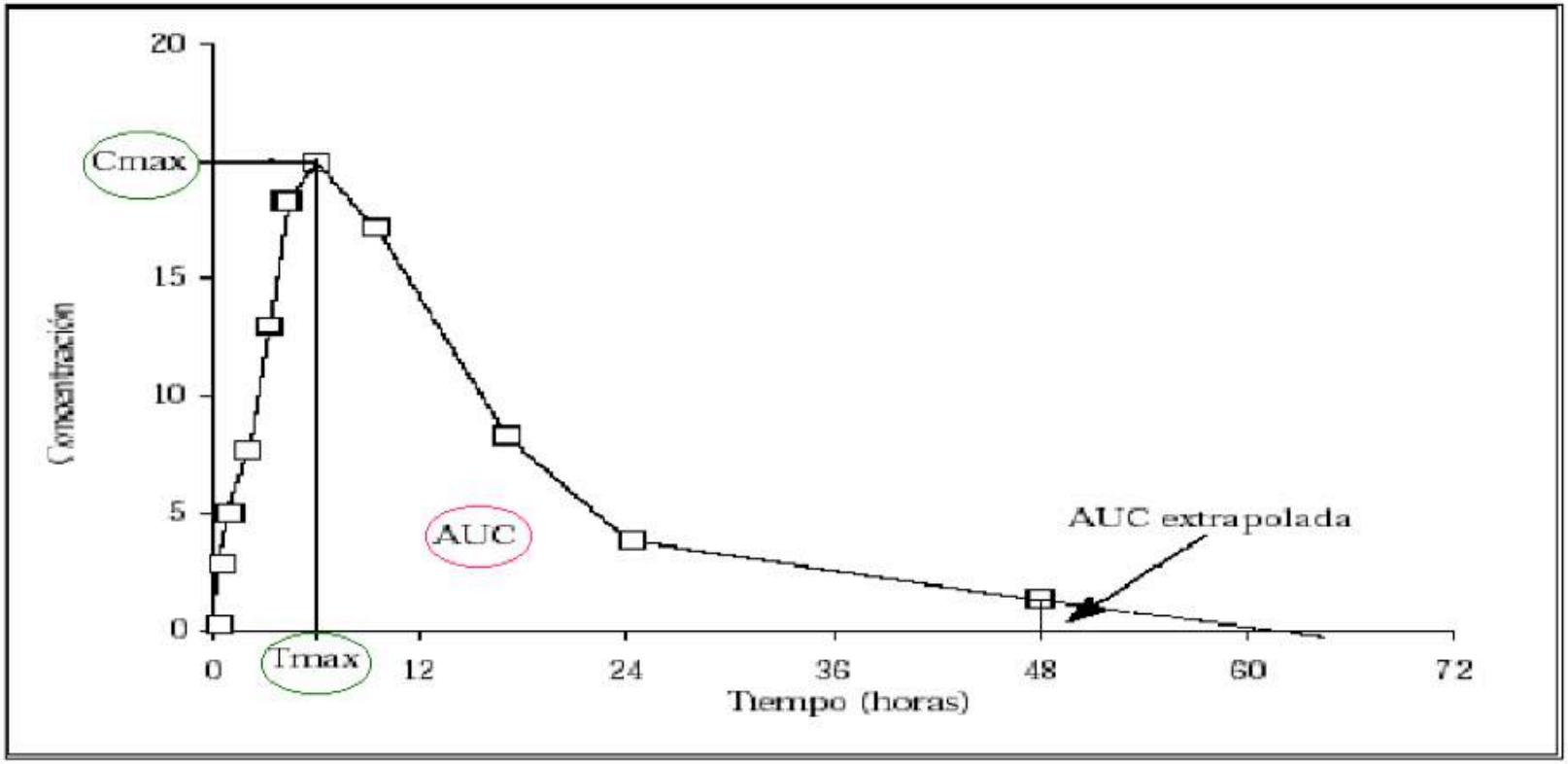


Principal parameters should show 90% confidence interval

Interval for AUC and Cmax of 80-125%

Tmax is a secondary parameter

Graphic representation

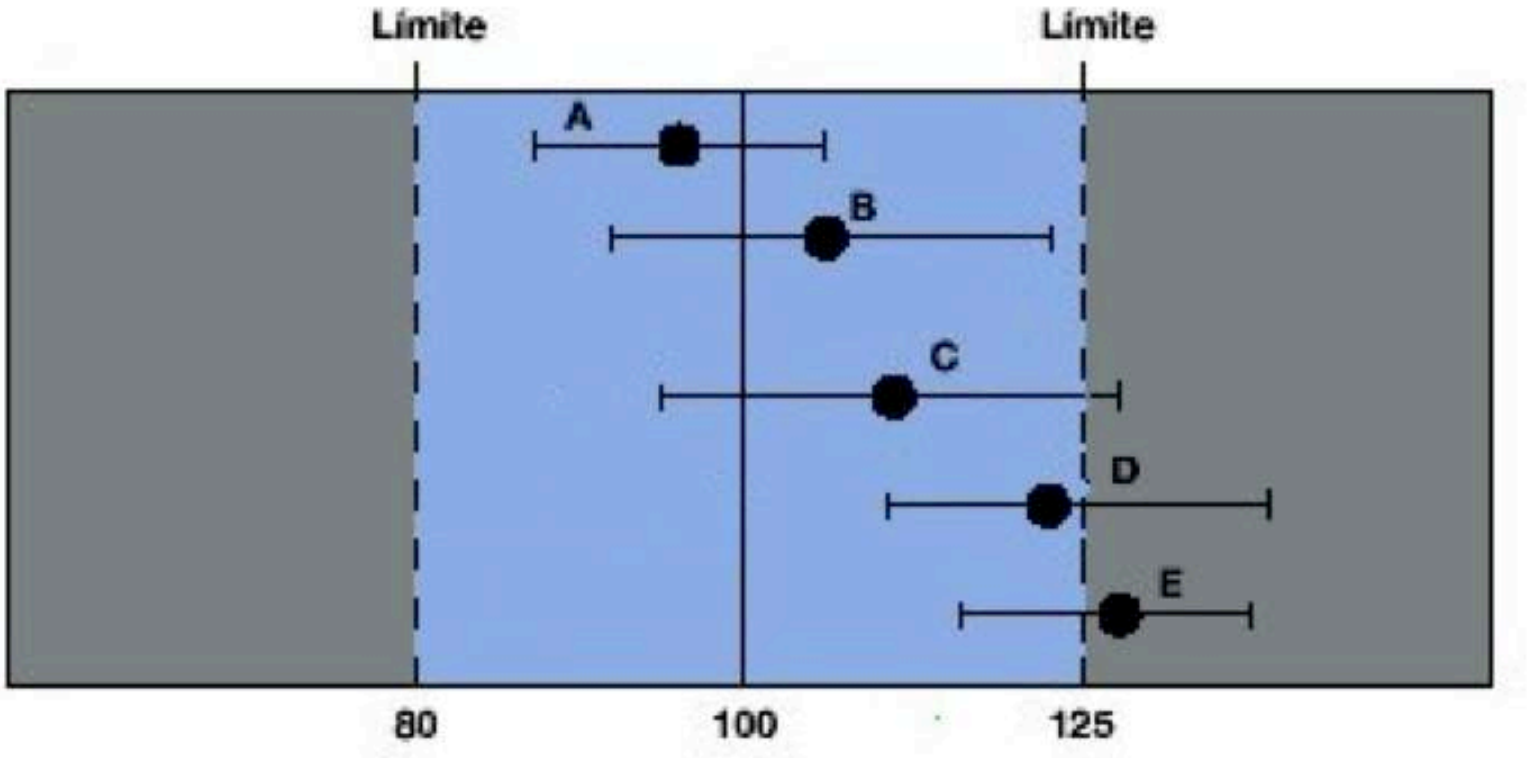


Two medicinal products are bioequivalent, if they present:

- Same quantity of active substance
- Same dosification form
- Same bioavailability after administration of same doses at identical conditions

Pharmacological effects are the same for both drugs.

Interpretation of results

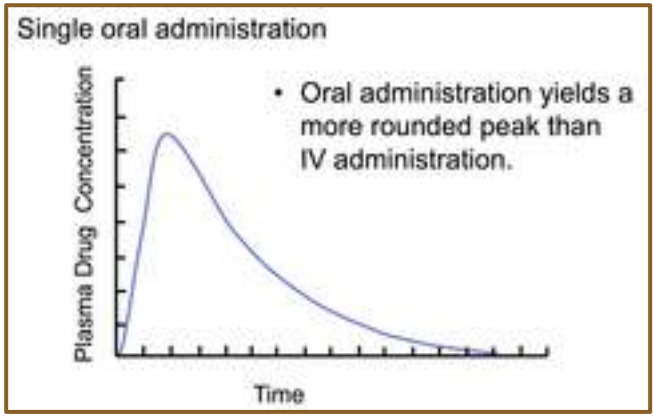


- **Bioequivalence Test (Media +- confidence interval 90%)**
- **A, B Bioequivalent**
- **C, D, E No bioequivalent**

Number of bioequivalence studies

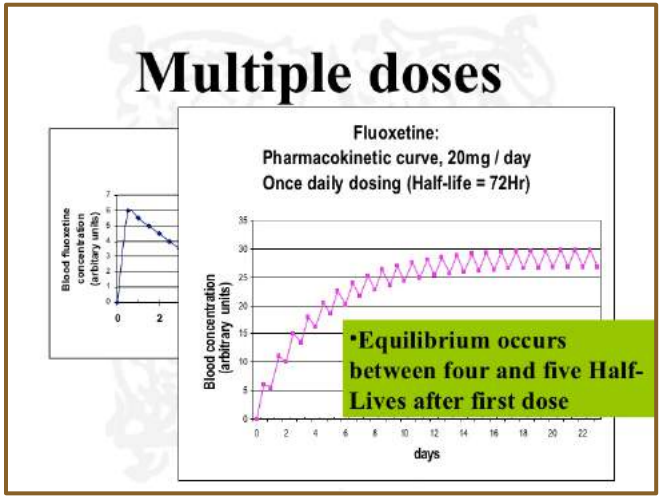
Immediate release form

- **One study for each strength**
  - **A partial bio-waiver of some strengths if they are proportional**
    - **If innovator is administered with food, the study will be in FED conditions**
    - **If innovator is administered without food, the study will be in FASTING conditions**



Prolonged-release form

- **Three studies for each strength if they are not proportional**
  - **Single-dose in fed conditions**
  - **Single-dose in fasting conditions**
  - **Multiple-dose** in fed or fasting conditions (depends on the **SmPC of innovator product)**



Exceptions for bioequivalence – CPMP/EWP/QWP/1401/98 Jan2010

- Aqueous oral solutions: if excipients do not affect GI tract, absorption, nor stability in-vivo of the active substance

- Parenteral solutions: aqueous IV solutions, solutions IM or SC of the same type (aqueous or oily)

- Inhalation gas

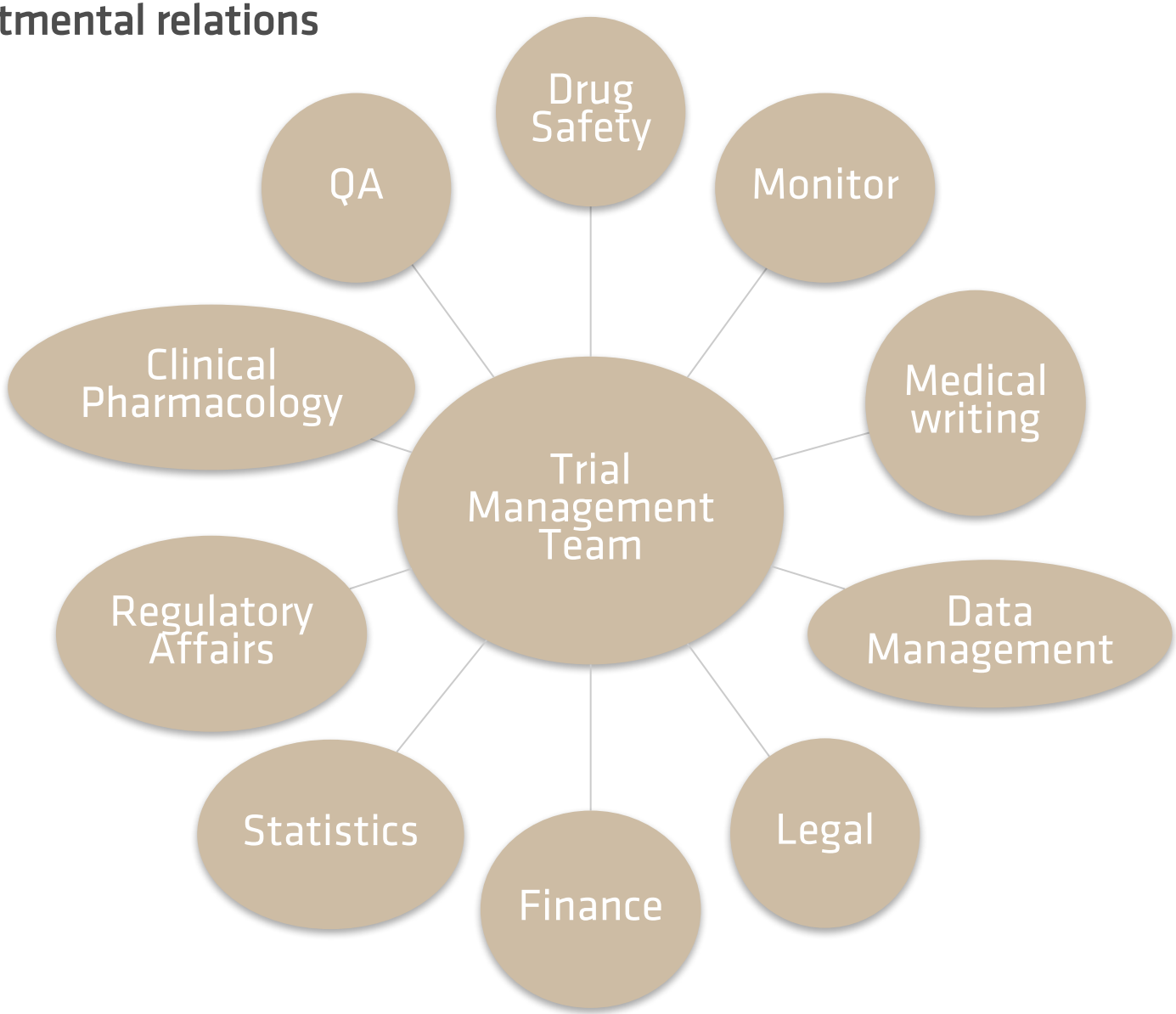
- Local action (nasal spray, inhalation, dermic, etc): without systemic absorption. Pharmacodynamic or Clinical comparative studies, or justification are required.

Department tasks and responsibilities - SPONSOR

- Protocol/ Informed consent/ Case Report form/ Investigator brochure (IB)
- Investigator/monitor selection
- Ethics Committee and Health Authorities approval
- Provide drug study medication
- Submit any serious adverse event occurred during study
- Provide insurance to patients participants
- Collection and Analysis of patient data
- Elaborate final report
- Publish results following transparency policy

Clinical Trial Team - Internal

Interdepartmental relations



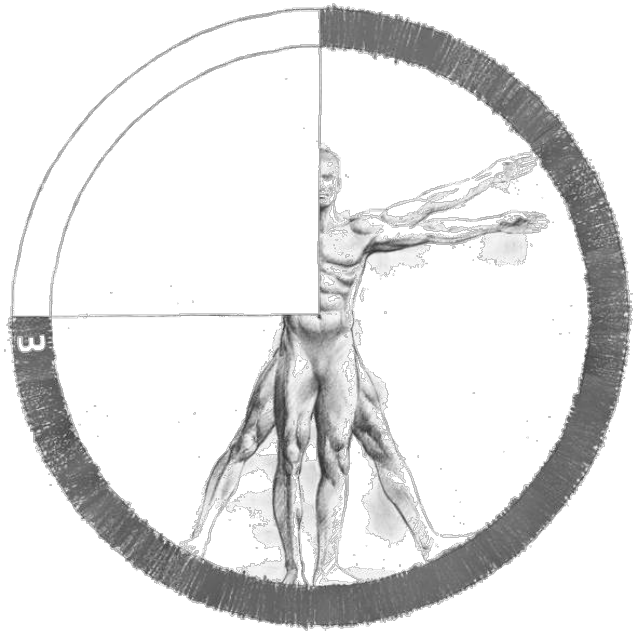
Clinical Trial Team - External

Interdepartmental relations

ONE DAY IN THE OFFICE

- **Best/worse of the job position**
- **What you have to lead with?**

- GENERICS COMPANY – HIGHT PRESSURE TO BE THE FIRST IN THE MARKET
- STRICT TIMELINES AND DEADLINES – PLANIFICATION AND PROJECT MANAGEMENT
- SUPERVISE THE CRO'S TASKS
- BE IN CONTACT WITH HEALTH AUTHORITIES
- DETAILED REVISION OF PROTOCOLS AND INFORMED CONSENT



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Background history

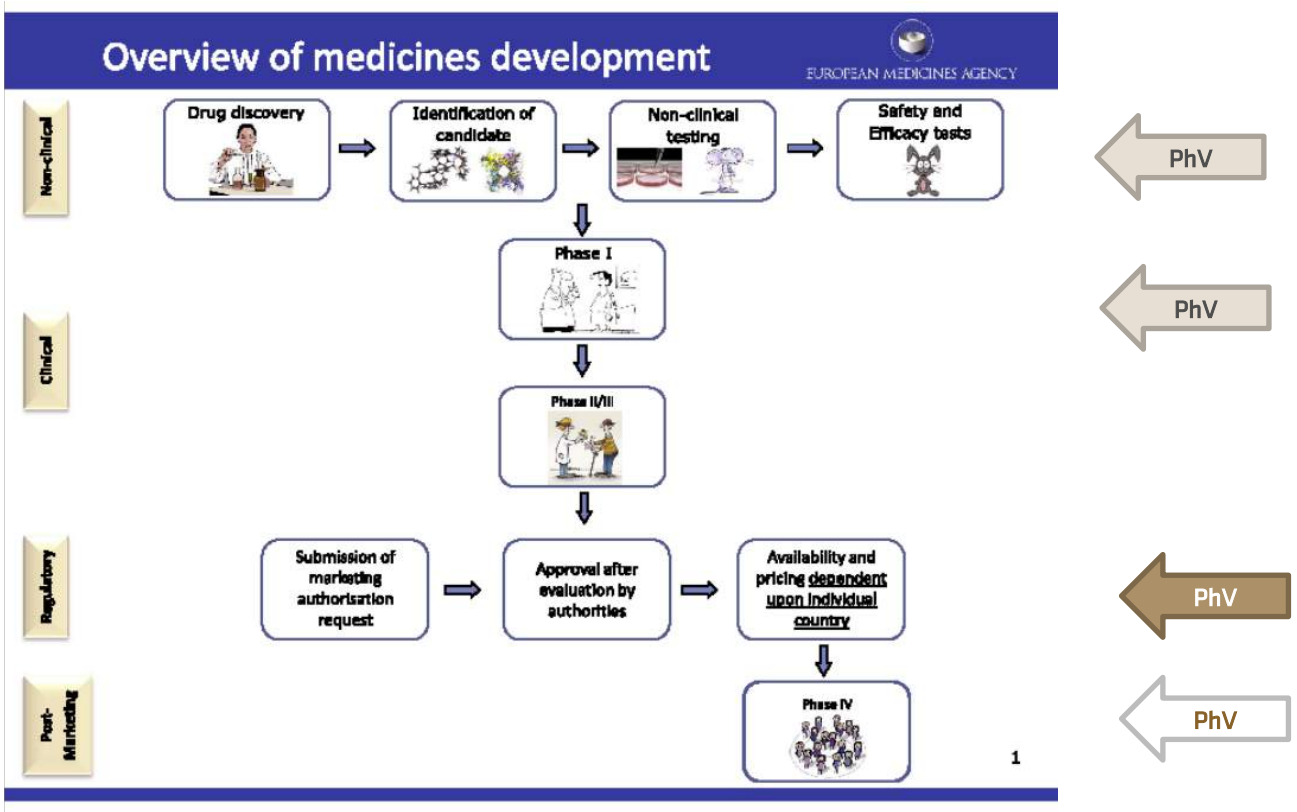
- 1937 – Renal failure by dietilenglicol/sulfamide elixir
- 1938 – FDA demands toxicological and preclinical controls for drug investigation
- 1950 – Cloranfenicol, causal agent of aplastic anemia
- 1960 – FDA initiates the collection of Adverse Drug Reactions in the Johns Hopkins H & Boston Collaborative Drug Surveillance Program: intrahospitalary monitorization.
- 1960-62 "**The talidomide disaster**" cases of focomelia (congenital malformation). The first case was published in Lancet (WG McBridel) suggesting a relationship with the thalidomide ingestion.

Thalidomide was withdrawn in 1962 after more than 4.000 cases were registered worlwide.

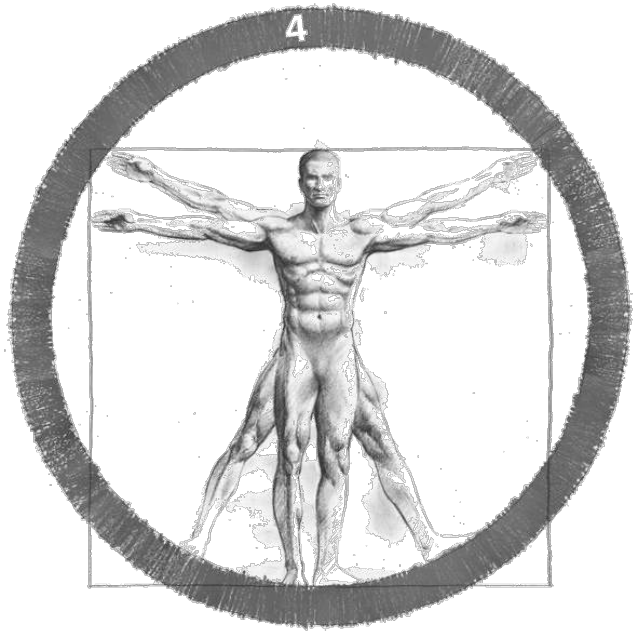
1962 WHO initiates an international program to collect and monitor adverse drug reactions.

Definition of Pharmacovigilance

- Pharmacovigilance: Detection, assessment and prevention of adverse drug reactions.



- Objective: optimise the benefit-risk balance of medicinal products



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WHAT IS THE MARKED LOOKING FOR? ARE YOU THE PERSON?

Personal skills for the job positon

- Attitude: self-motivated, easy learning, multi-task and decisive
- **Organised, tidy, responsible and focused**
- Search engine, resolutive and flexible

Previous Knowledge

- Graduate in Health Science, preferibly Pharmacy (Medicine, biology, biomedicine, biochemistry, etc)
- Normally, post-graduate focused in Pharmaceutical Industry is required, including intership.
  For example, CESIF, UB, ESAME, etc.
- High English level

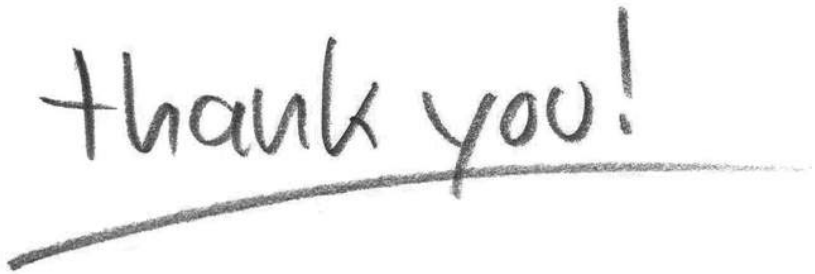
CAREER DEVELOPMENT

High quality Future opportunities

- Clinical, Pharmacovigilance and Regulatory affairs.
- Technical and high specialization in Generics valued by the company.

Knowledge development

- In vivo studies – Bioequivalence studies – Fase I
- In vitro studies – Dissolution Profiles
- Pharmacokinetics & Pharmacodinamics
- Scientific Bibliographical search – Medial writing
- Pharmacovigilance


thank you!