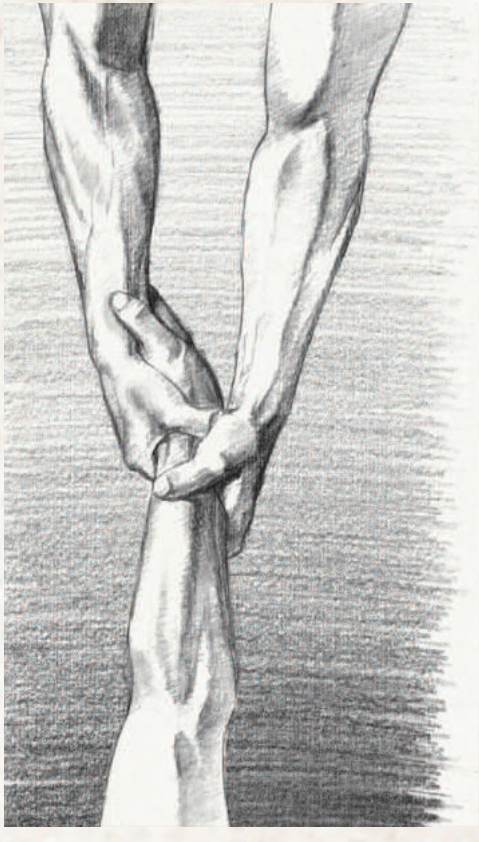
Clinical and Drug Safety

Workshop University of Barcelona- 15 March 2017

Griselda López

believe in life
Galenicum

Presentation



GALENICUM HEALTH S.L.

- We are a young innovative oriented company (development of generics)
- Offices in Perú, Chile, Brazil, Colombia, China, Malta and Barcelona
- Different business models B2B and B2C

GRISELDA LÓPEZ

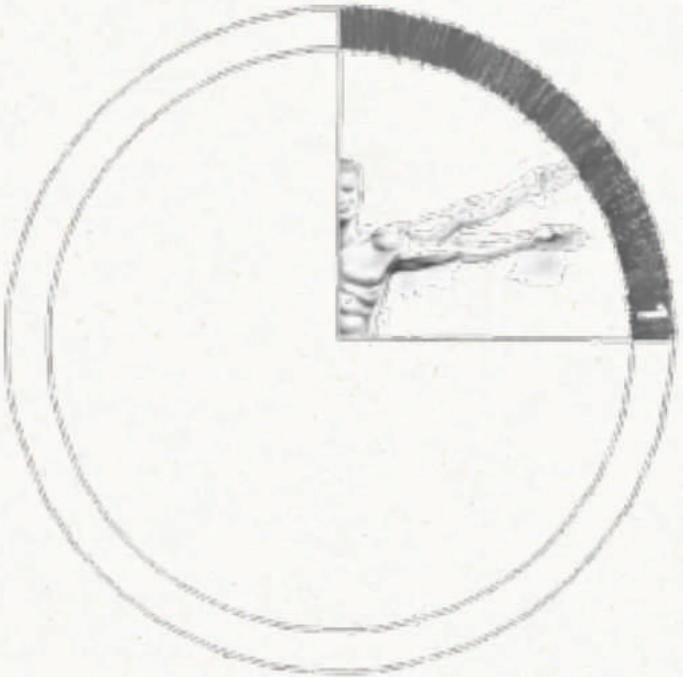
- Graduated in Pharmacy by the University of Barcelona
- Post-graduated in Pharmaceutical and Parapharmaceutical Industry by CESIF
- Post-graduated in Monitoring of Clinical Trials by ESAME
- Specialised mainly in Regulatory Affairs, Clinical Trials (BQ) and Pharmacovigilance.
- Professional Experience in Galenicum since 4 years ago

Clinical Trials

Generic-Bioequivalence studies

Pharmacovigilance

Career development/skills



Clinical Trials

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Introduction to Clinical Trials

DEFINITION – Clinical Trial:

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."

Introduction to Clinical Trials

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.

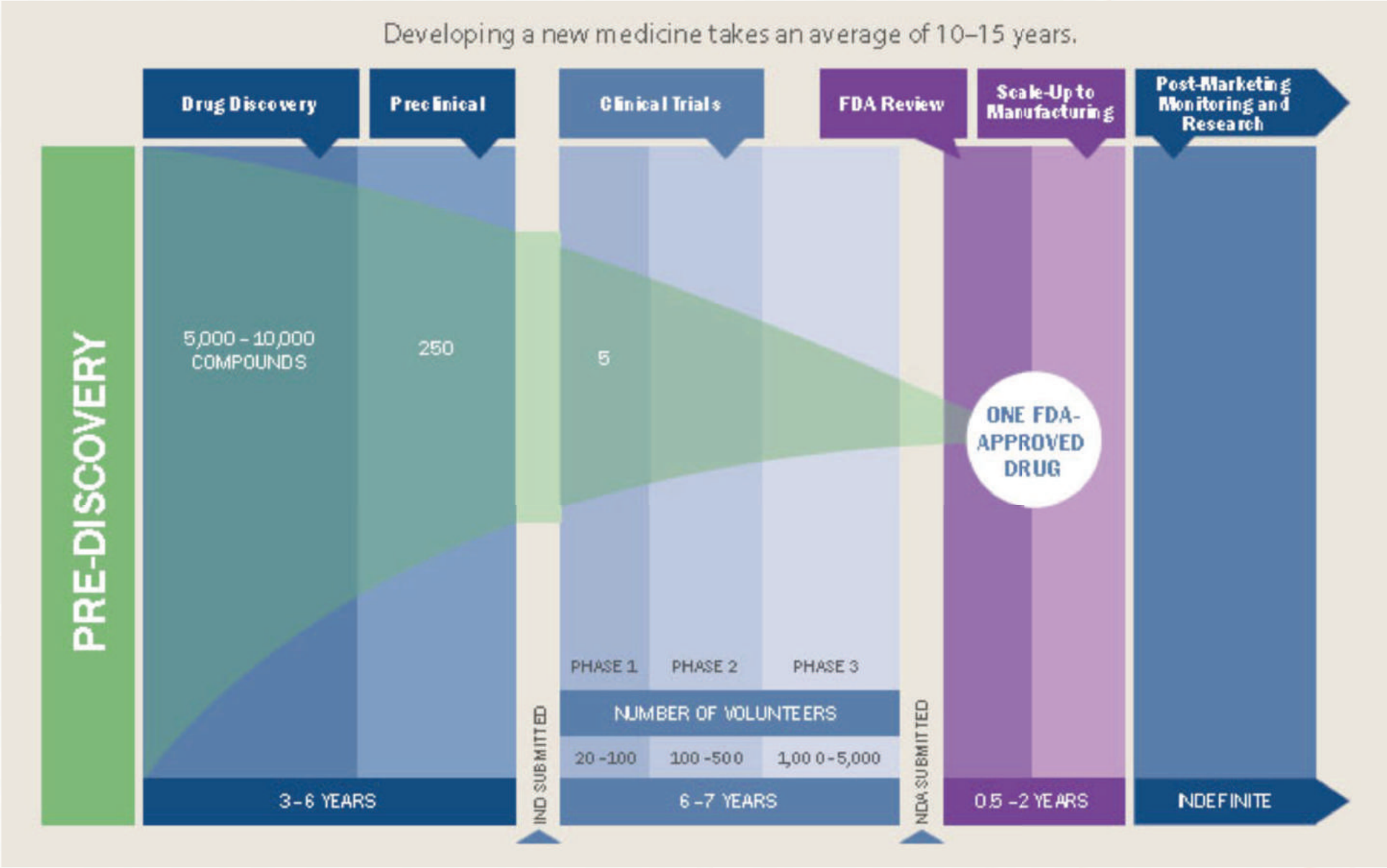
International Conference Harmonisation (ICH)

Directive 2001/20/EC

Regulation EU No 536/2014

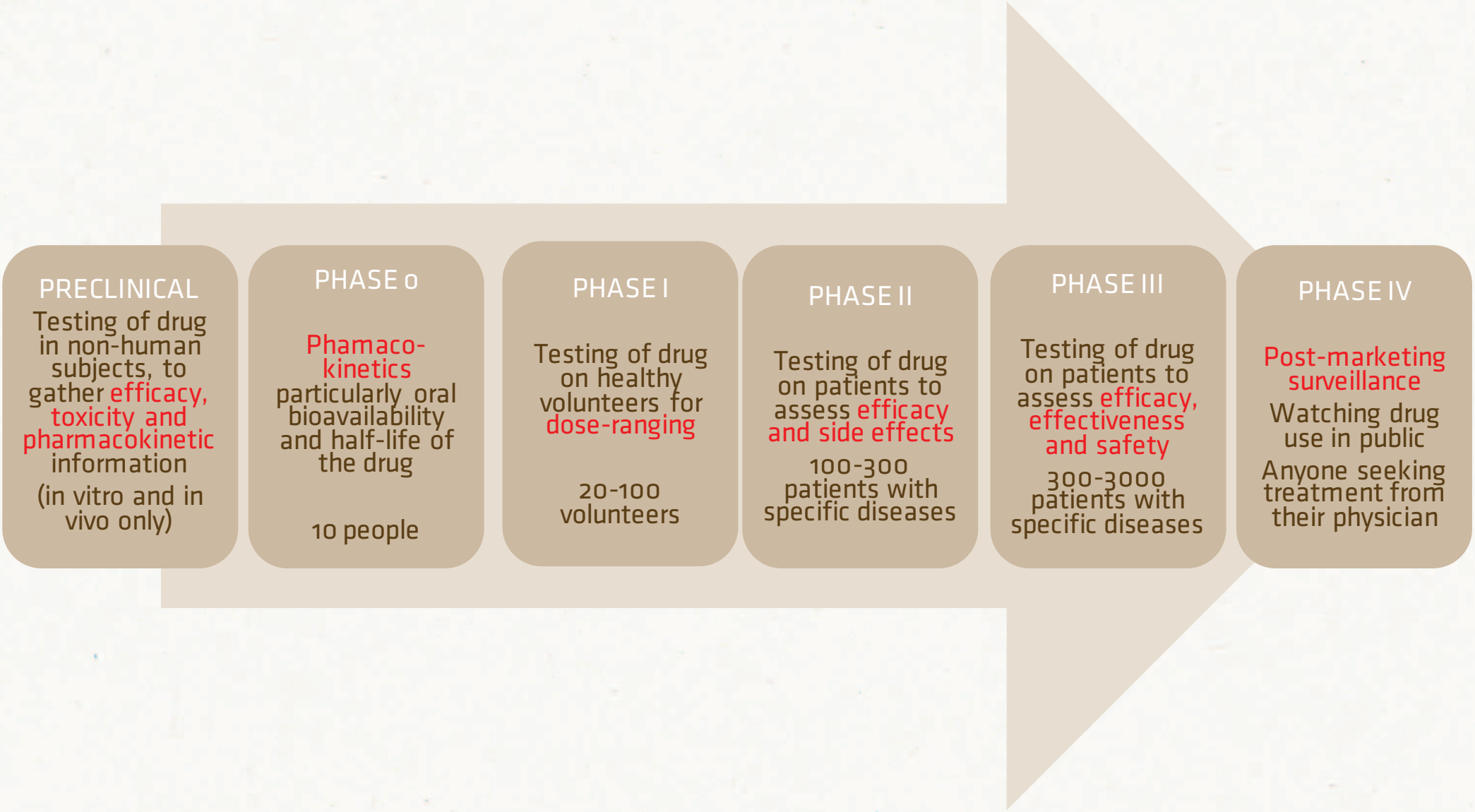
Real Decreto 1090/2015

The research and Development Process

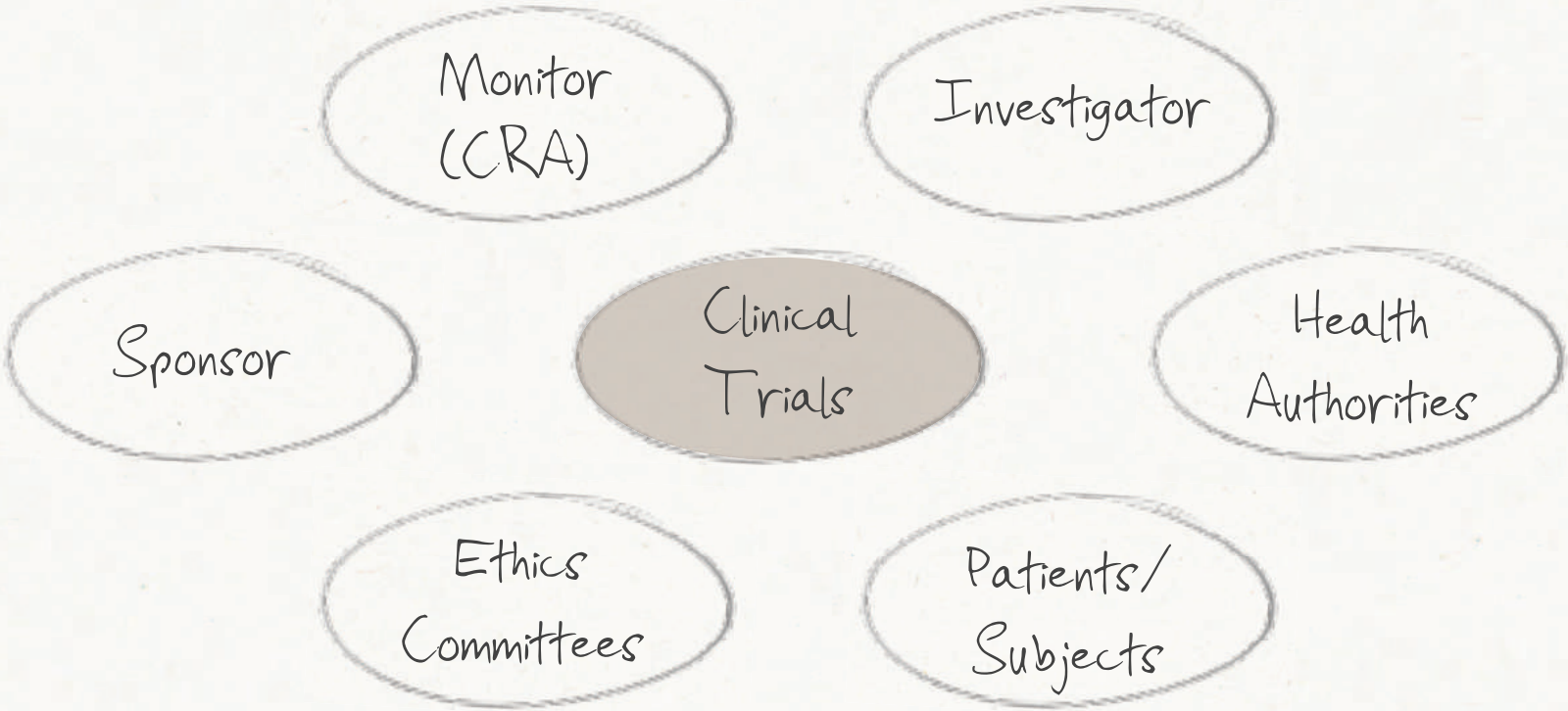


SOURCE: Pharmaceutical Research and Manufacturers of America, Drug Discovery and Development (www.innovation.org)

Summary of clinical trial phases



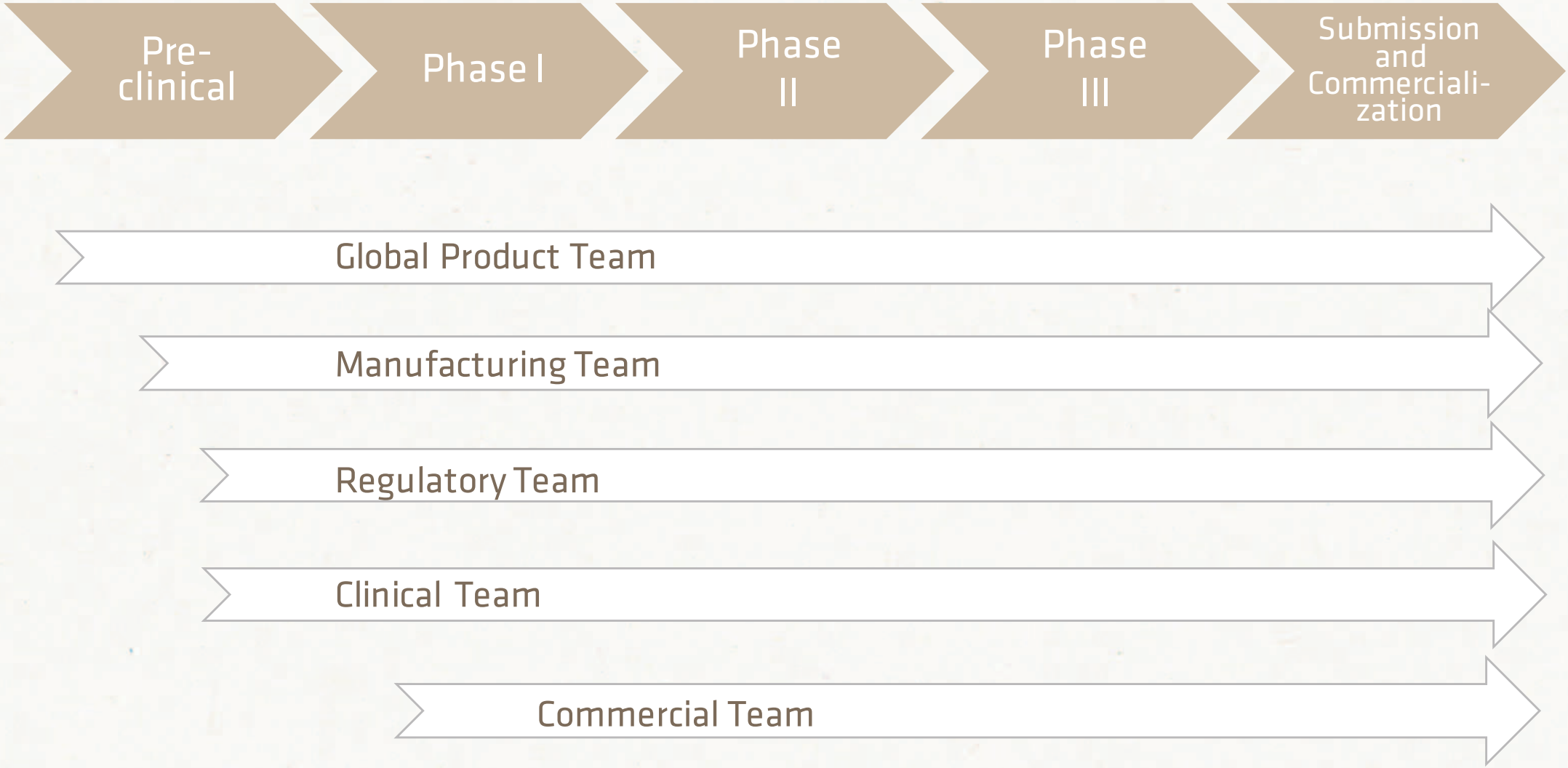
Stakeholders in Clinical Trials



Department tasks and responsabilities - SPONSOR

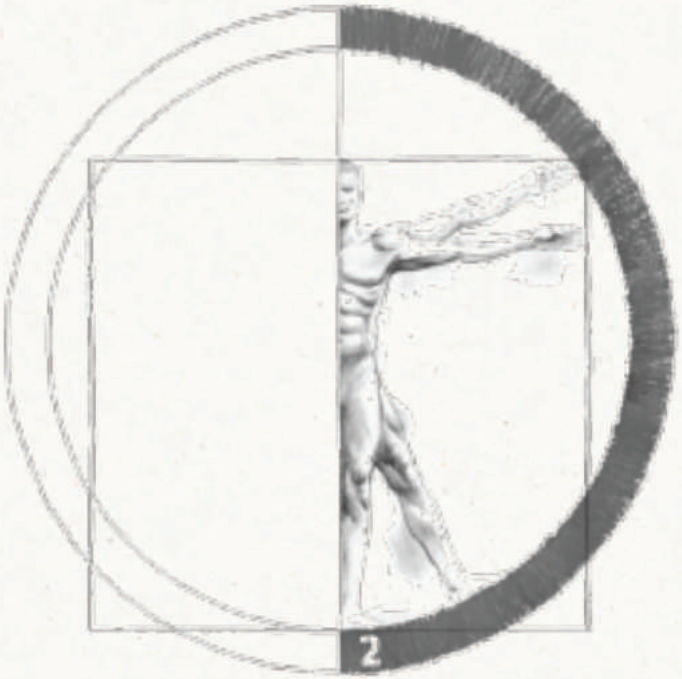
- Protocol/ Informed consent/ Case Report form/ Investigator brochure (IB)
- Investigator/monitor selection
- Ethics Committee and Health Authorities approval
- Provide drug study medication
- Submit any serious adverse event occurred during study
- Provide insurance to patients participants
- Collection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

Summary of clinical trial phases



Clinical Trial team - Internal

Clinical Trial team - External



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Definición MEDICAMENTO GENÉRICO

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)

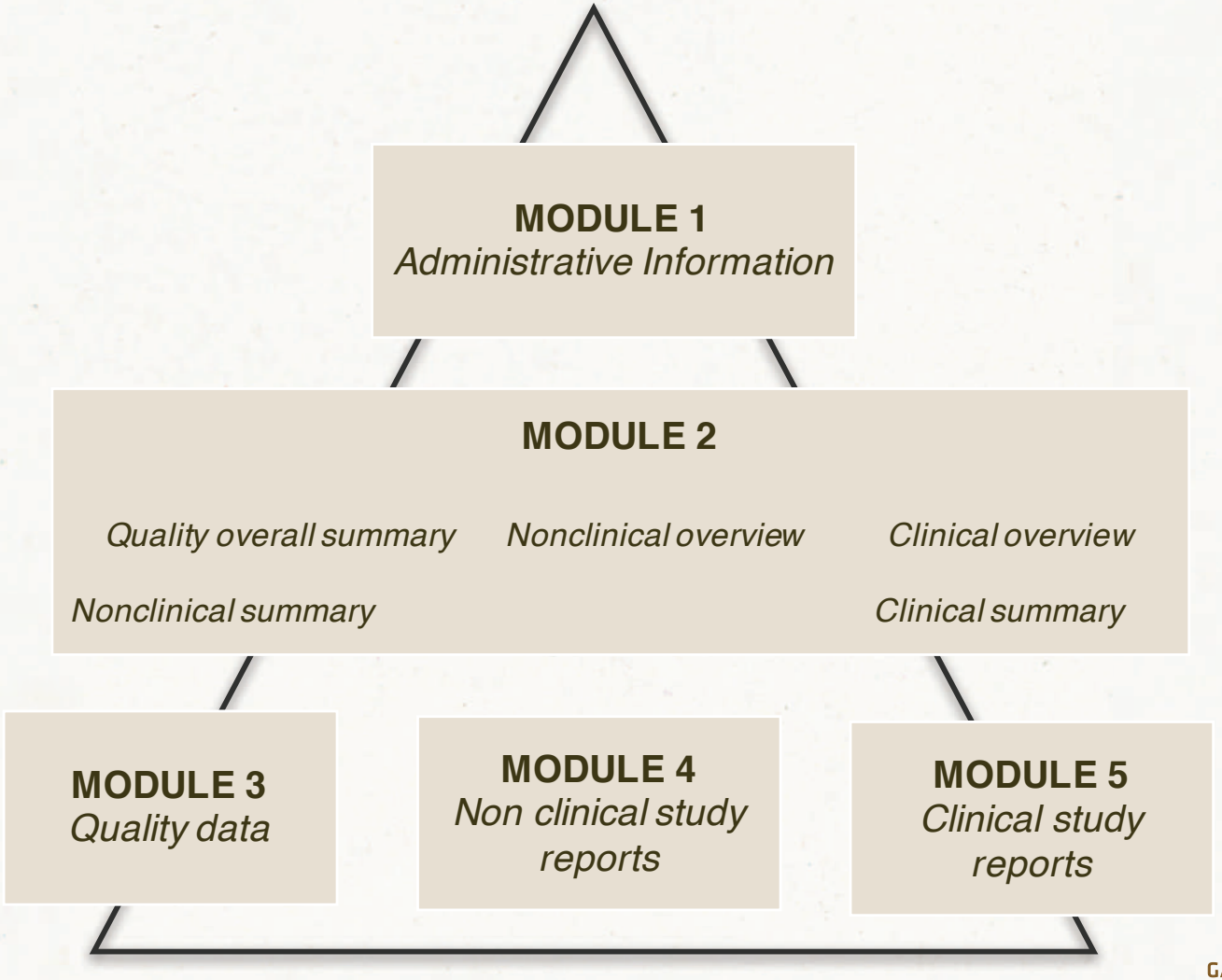
✓ Apariencia (color, tamaño, forma, sabor, embalaje)

✓ Laboratorio fabricante (puede ser el mismo)

Registration Dossier: Common Technical Document (CTD) format)

TYPE OF DOSSIERS:

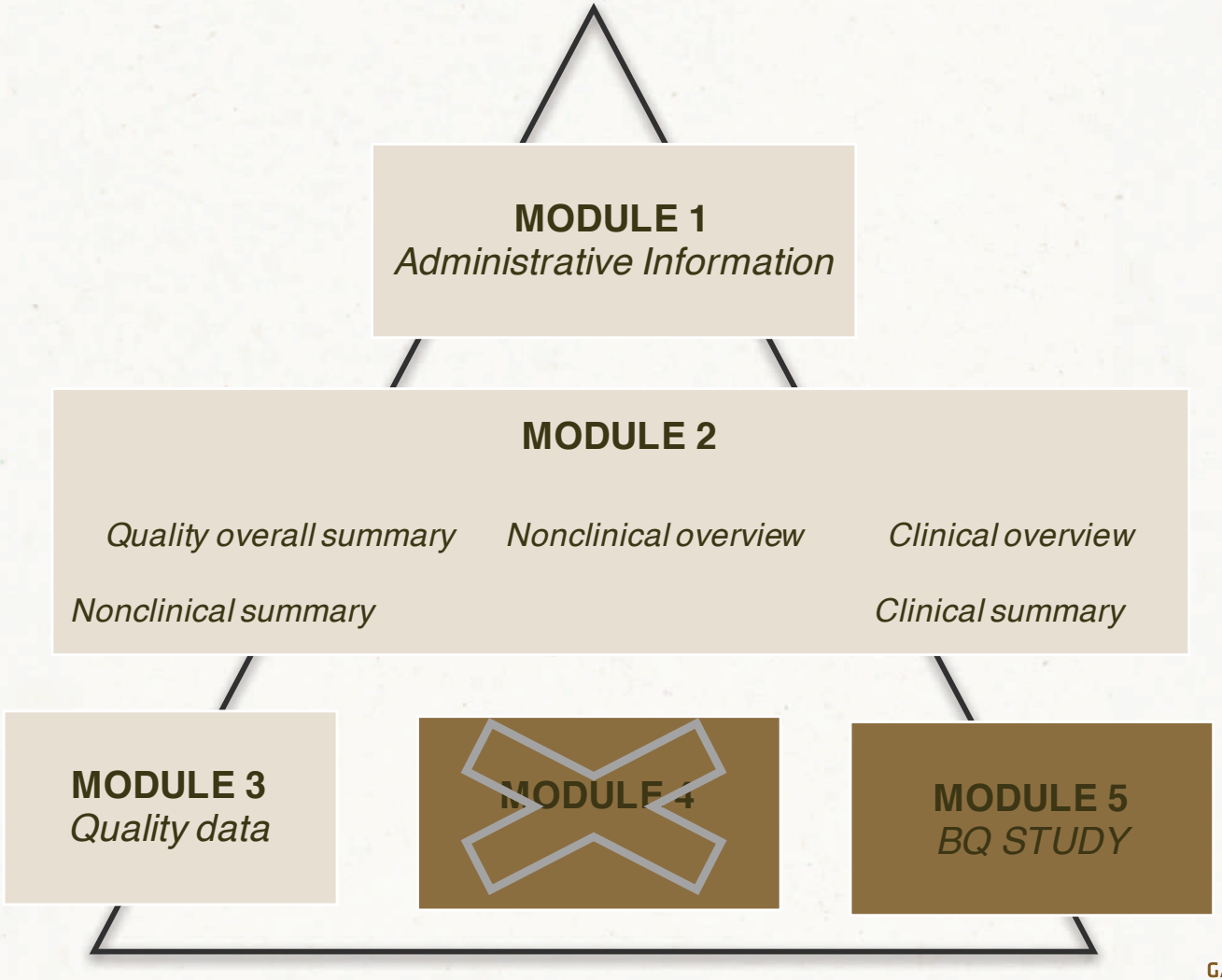
1. COMPLETE/STAND-ALONE: Innovator (Art 8.3) or Bibliographical (Art. 10a)



Registration Dossier: Common Technical Document (CTD) format)

TYPE OF DOSSIERS:

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



GENERIC PRODUCT: Bioequivalence

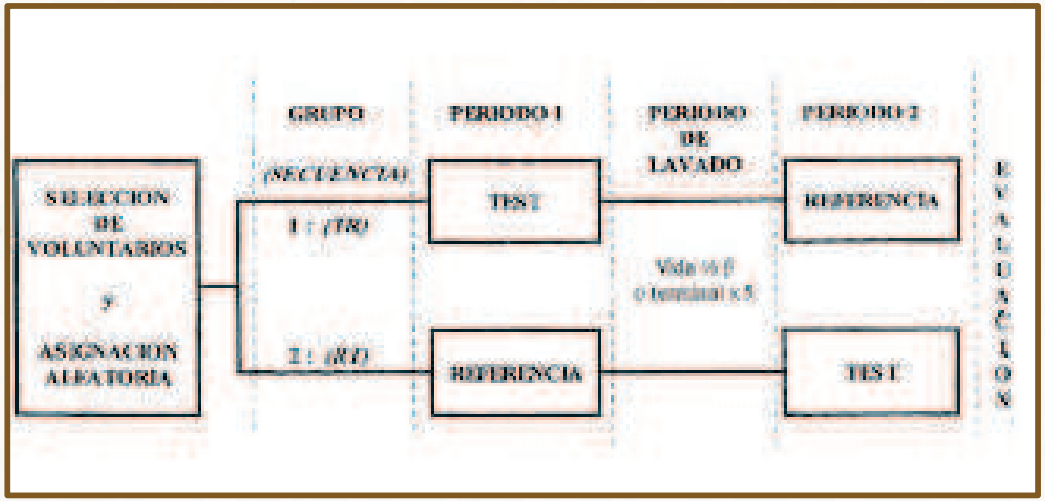
BIOEQUIVALENCE based on CPMP/EWP/QWP/1401/98, Jan 2010:

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

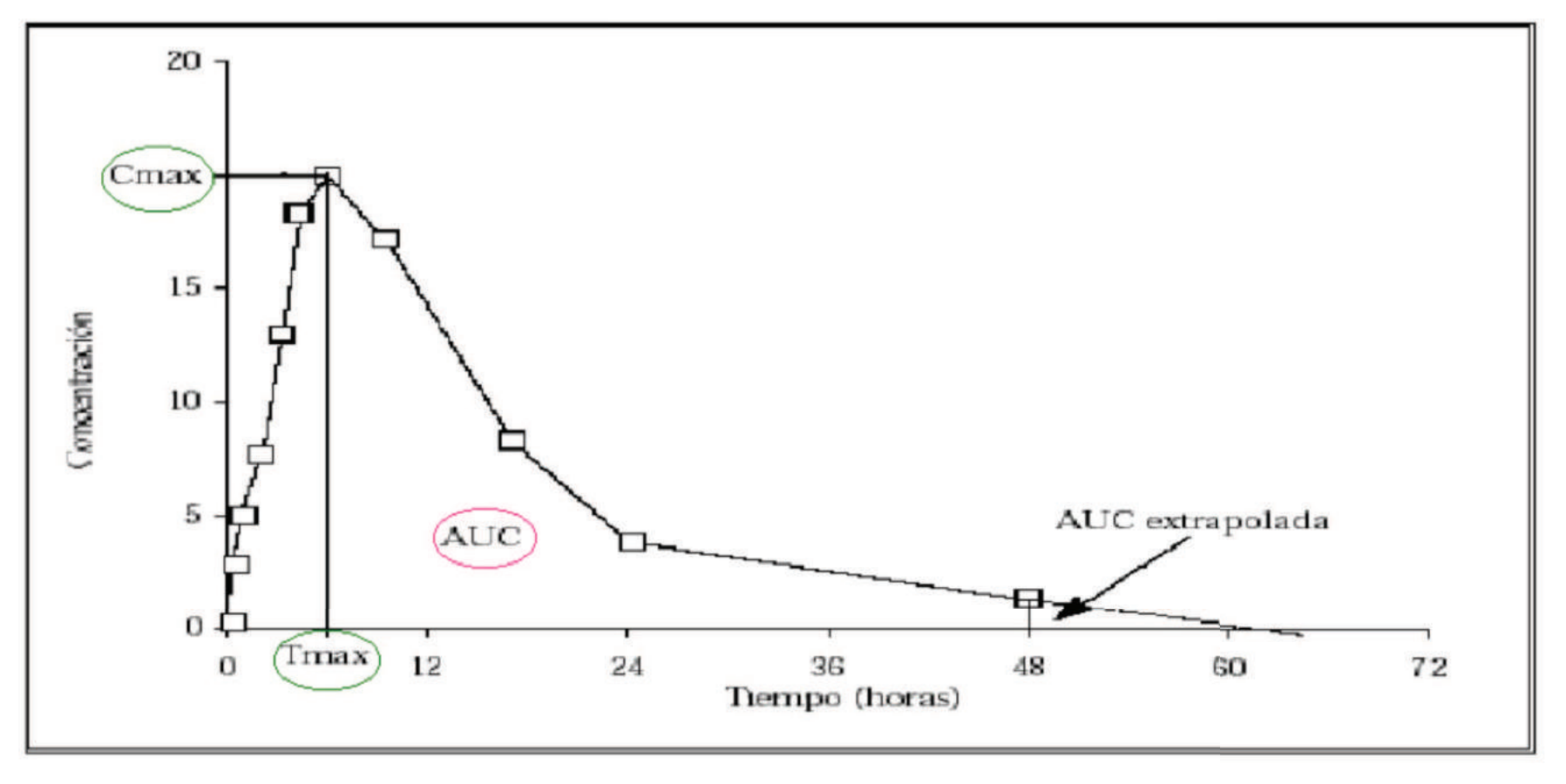


Principal parameters should show 90% confidence interval

Interval for AUC and Cmax of 80-125%

Tmax is a secondary parameter

Graphic representation

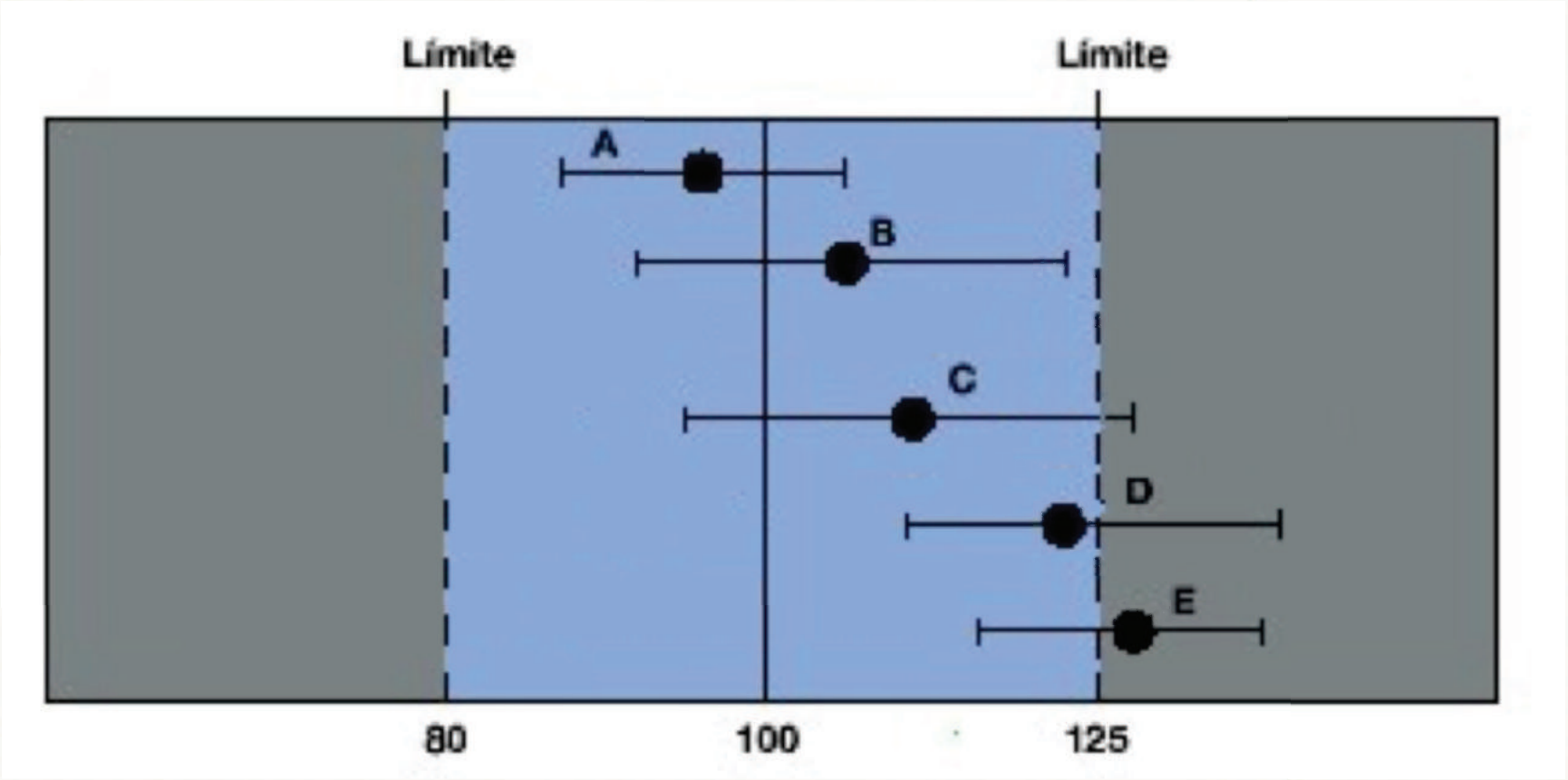


Two medicinal products are bioequivalent, if they present:

- 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

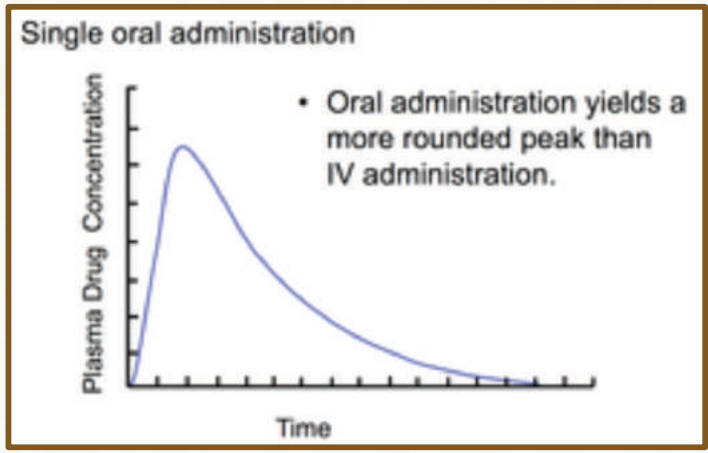


- Bioequivalence Test (Media +- confidence interval 90%)
- A, B Bioequivalent
- C, D, E No bioequivalent

Number of bioequivalence studies

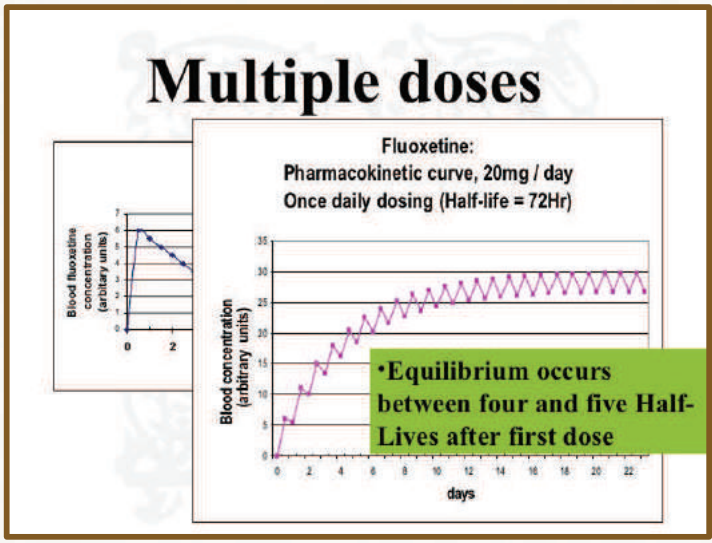
Immediate release form

- 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)



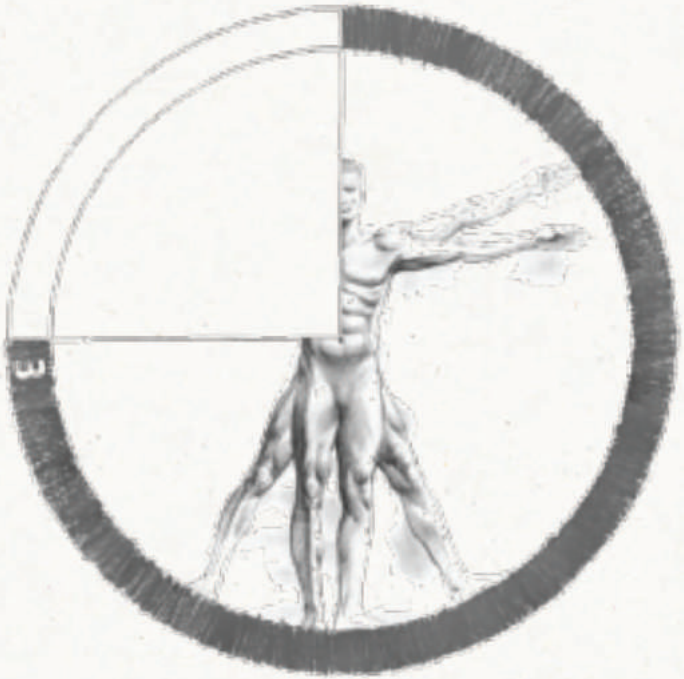
Exceptions for bioequivalence – CPMP/EWP/QWP/1401/98 Jan2010

- 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.



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Definition - PHARMACOVIGILANCE

Public health activity with the main objective of identification, quantification, evaluation and decision taking in front of the presence of drug risks once are marketed.

Good Pharmacovigilance Practices (GVP):

A set of measures drawn up to facilitate the performance of pharmacovigilance in the European Union (EU). GVP apply to:

- marketing-authorisation holders
- European Medicines Agency
- Medicines regulatory authorities in EU Member States.

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.

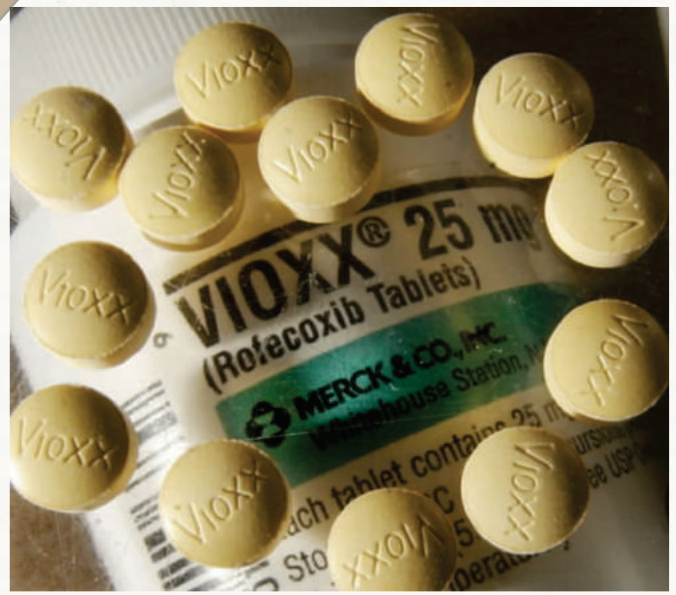
1962 WHO initiates an international program to collect and monitor adverse drug reactions.

Pharmacovigilance – Adverse reactions

It is a key public health function WHY?

- Unexpected adverse reactions
- Interactions
- Dependence
- Long term efficacy, Resistance
- Risk factors, etc

Approved by FDA in 1999 for arthritis.
Withdrawn by Merck on 2004 due to increased risk of heart attack and stroke associated with long-term, high-dosage use.



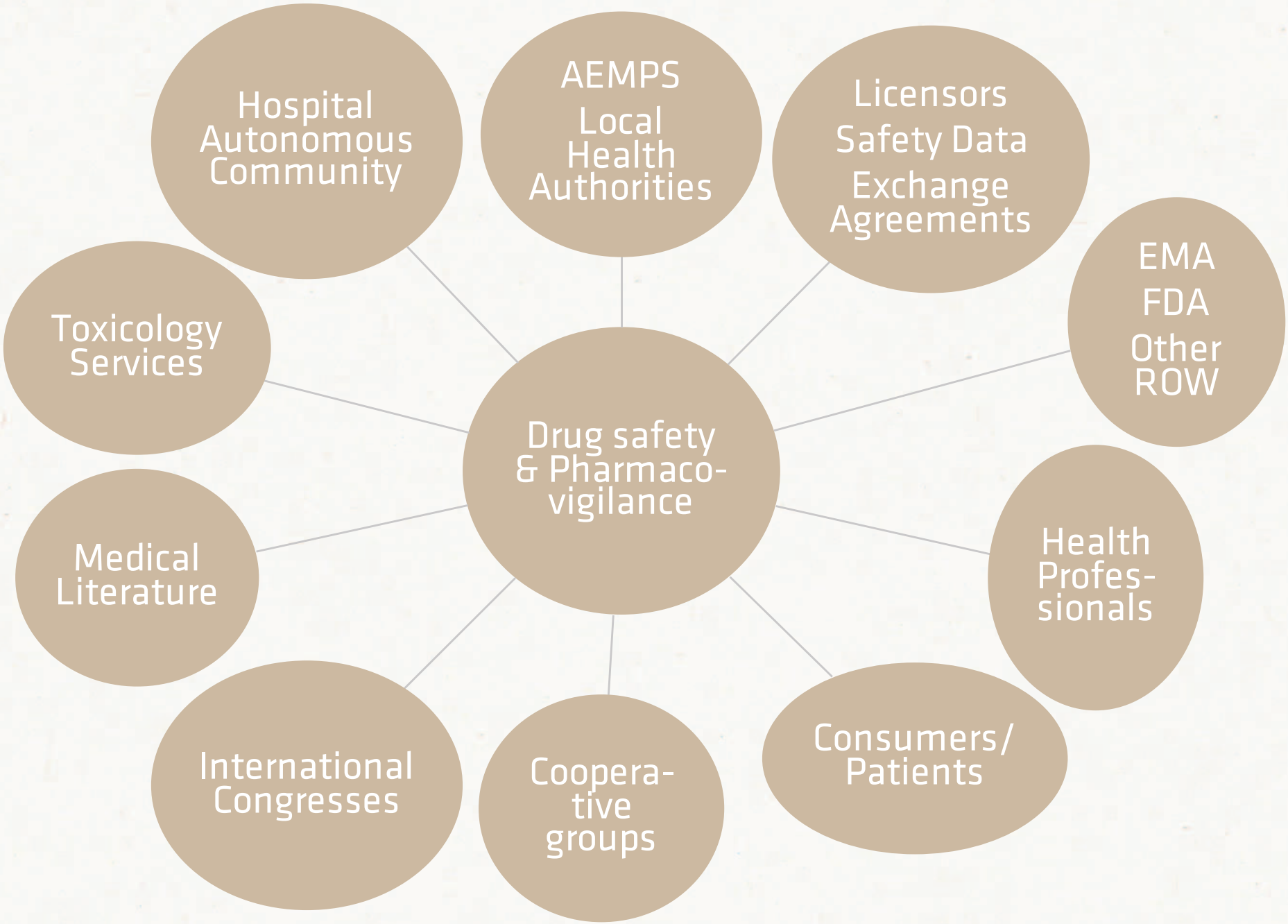
88,000 and 140,000 cases of serious heart disease of which roughly half died.
In the year before withdrawal, Merck had sales revenue of US$2.5 billion from Vioxx

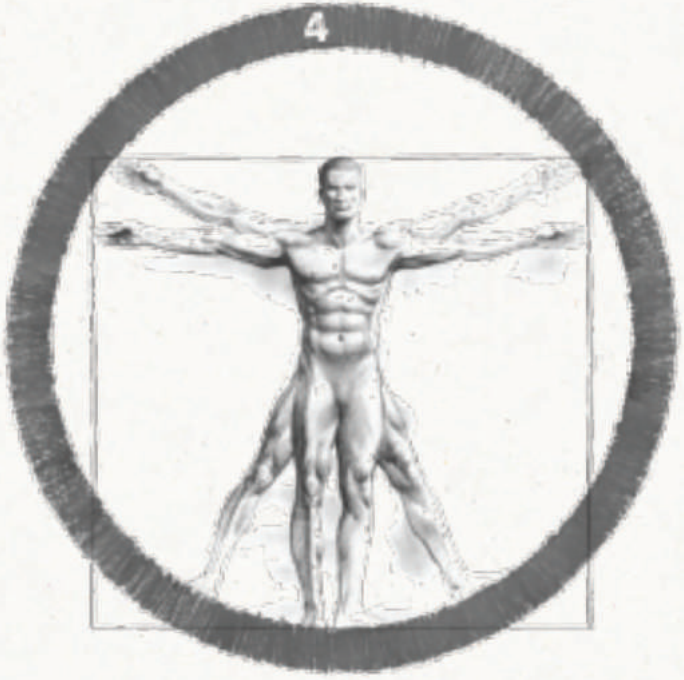
Drug Safety tasks and responsabilities

- Pharmacovigilance System Master File (PSMF) of the company
- Individual Case Safety Reports management
- Periodic Safety Update Reports (PSUR)s creation
- Labelling
- Risk Management Plan (RMP) elaboration
- Benefit/Risk evaluation
- SOP creation and update
- Safety Data Exchange Agreements (SDEA)
- Training of sales network and company employees audits

Pharmacovigilance- Internal interfaces

Pharmacovigilance- External Interfaces





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Career development & Personal skills for Clinical Department

Career

- 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

Skills

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

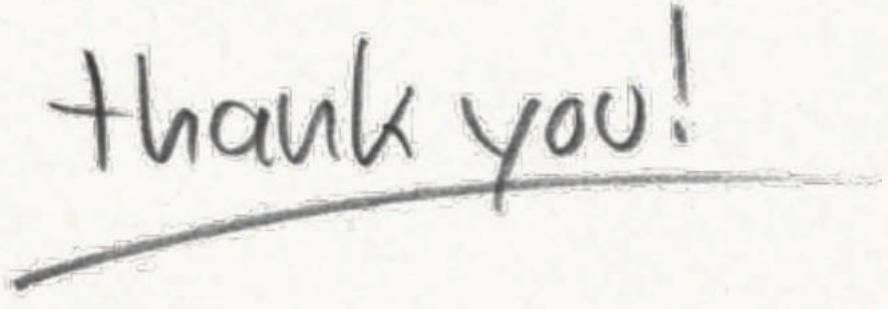
Career development & Personal skills for Clinical Department

Clinical development

- Operational aspects of clinical trials: monitor/CRA
- Regulatory: regulatory and GCP compliance
- Medical writing and publication
- Data management and statistics

Core competencies

- Good leadership, analytical, problem solving and time management skills
- Team work
- Negotiation skills
- Conflict management
- Familiar with basic computer and database applications
- Comunication skills



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