Introduction to clinical trials

José Sánchez 2020-01-22

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Definition of a clinical trial

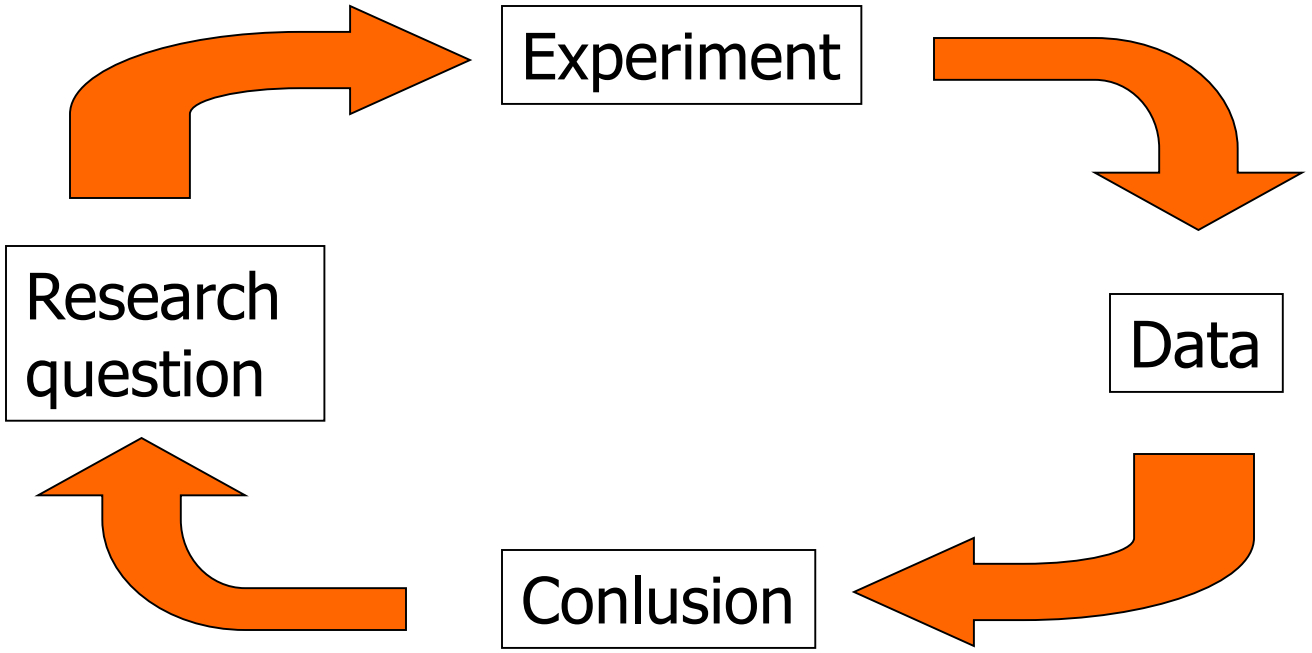
A research activity that involves administration of a test treatment to some experimental unit in order to evaluate the treatment.

Meinert, 1986.

Key words

Treament	Pharmaceutical, diet, procedure, diagnostic, device, program, placebo.
Experimental unit	Subject from a target population.
Evaluate	Assessment of (clinical) effect, but also adverse events, lab variables, vital signs, quality of life, health economy.

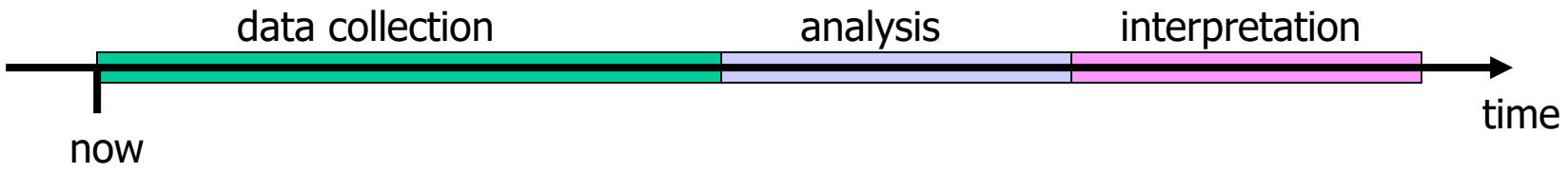
The Wheel of Science



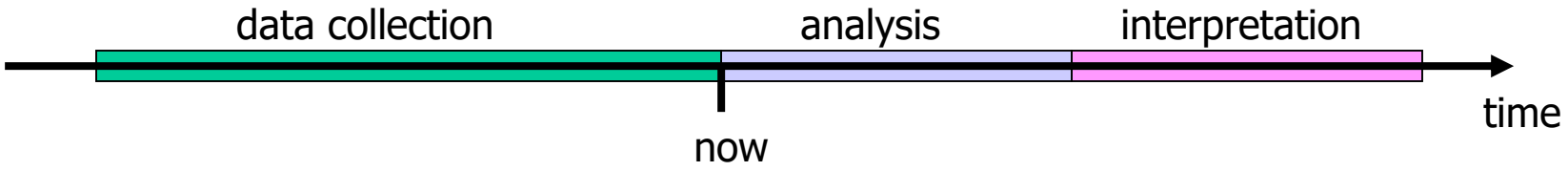
Observational studies

Data is collected for a set of patients without any randomisation

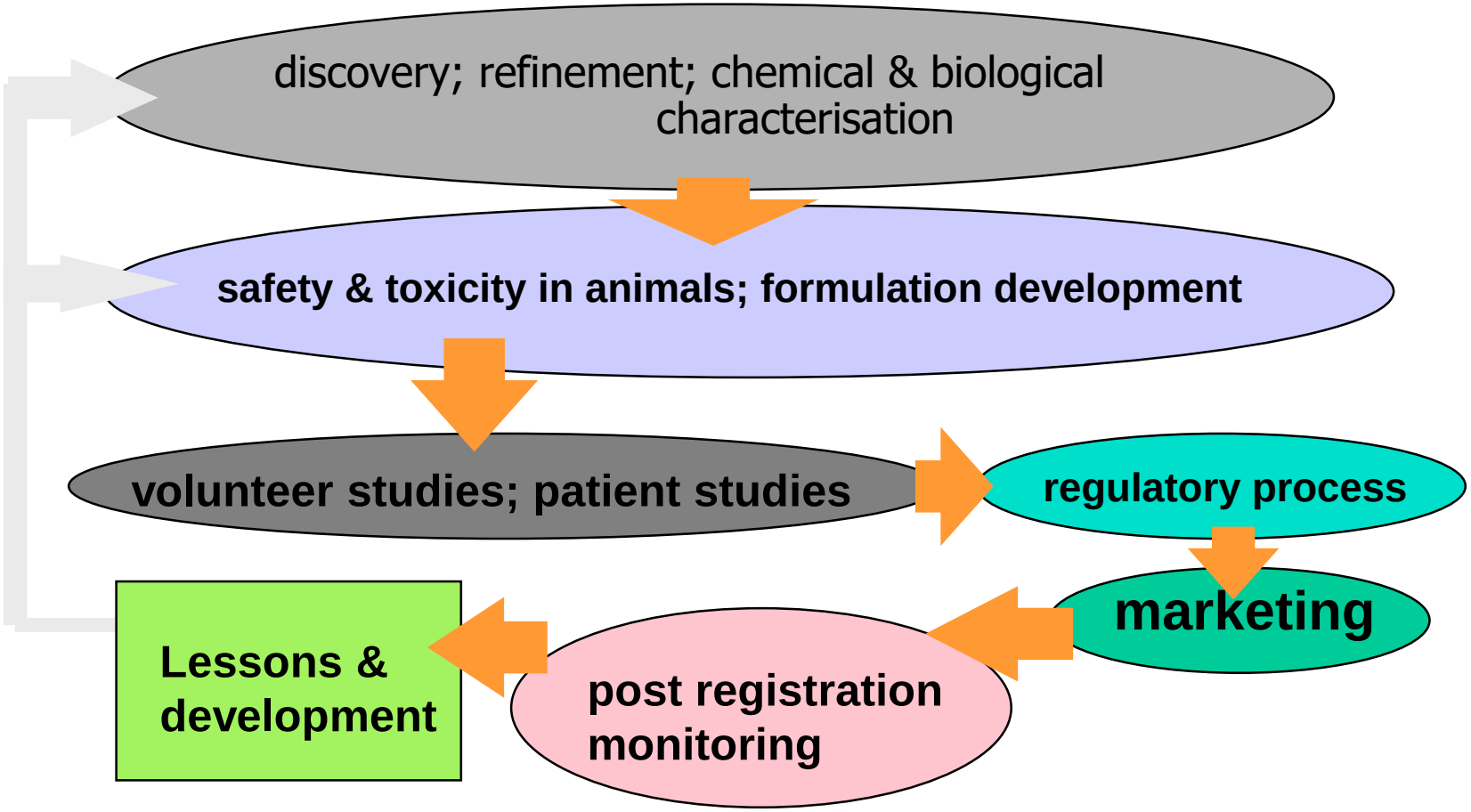
Prospective: Data is collected after the objectives are set



Retrospective: Data is collected before the objectives are set

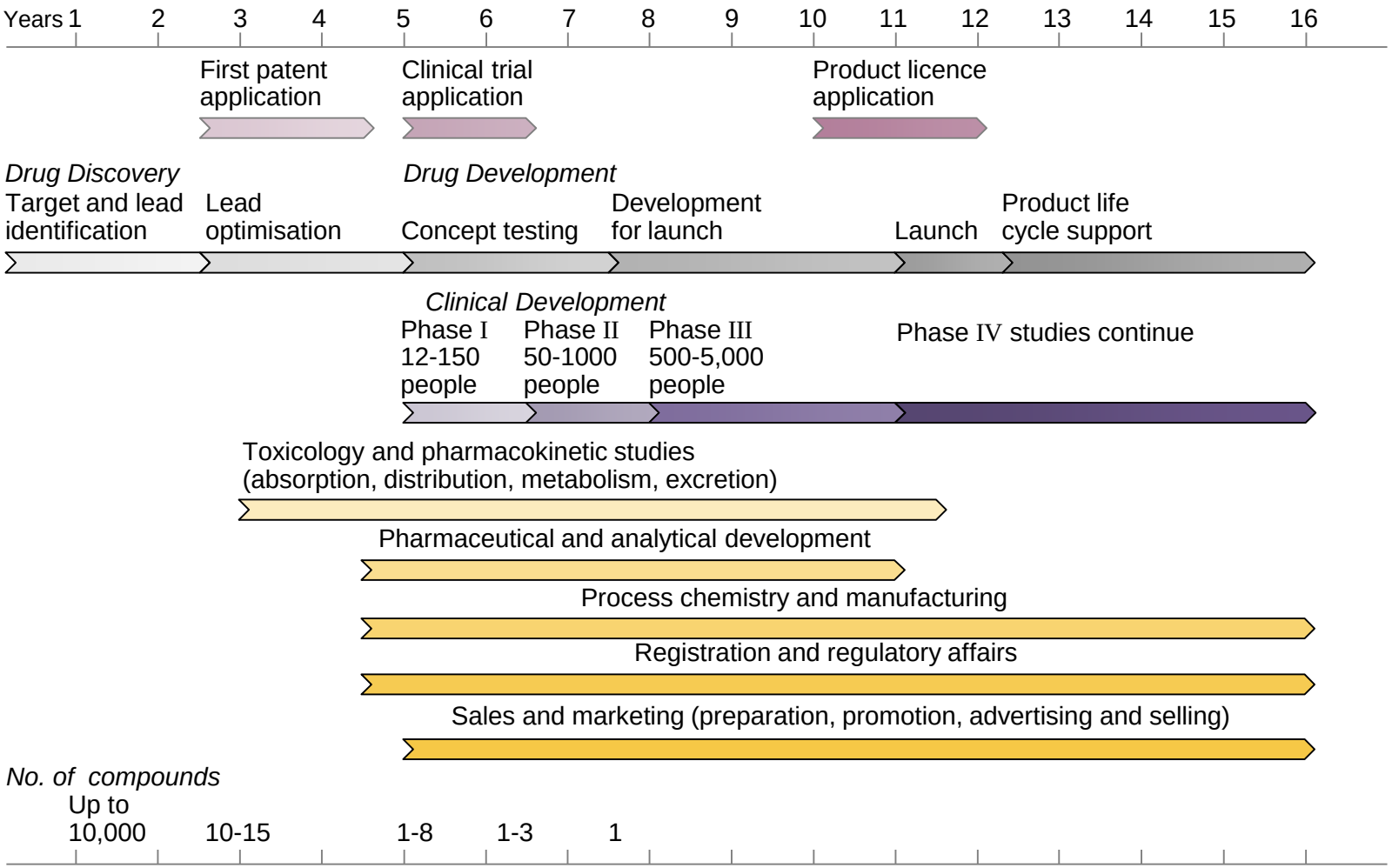


Drug discovery/development process



Discovery=find new active structure : Development=convert it to a useful drug

The path to a new medicine



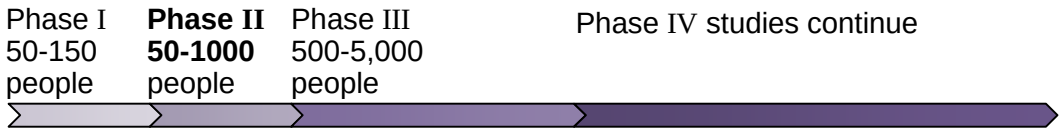
Regulatory processes and requirements

- Different for different regions.
- Similar for the U.S. (FDA), EU (EMEA) and Japan (PMDA).
- Clinical development divided in phases accepted by the FDA since the late 1970s.

Phase I trials

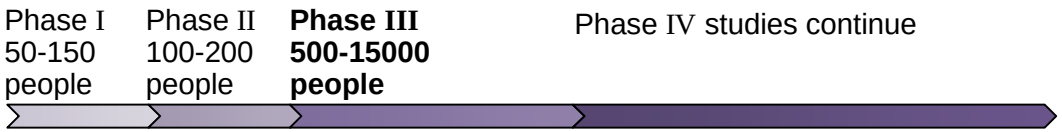
- Focused on tolerability and safety
- Pharmacokinetics
- 12-30 (150) healthy people (often males)
- Efficacy on biomarkers (Explorative)
- Single and repeated doses (SAD and MAD)
- Increase dose levels
- Interaction with other drugs
- Explorative

Phase 2 trials



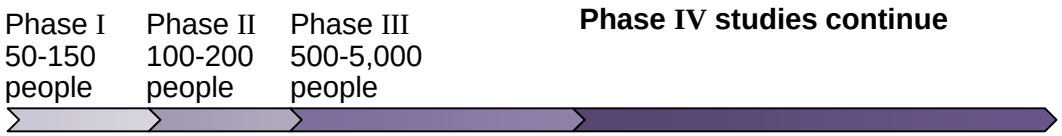
- 50-1000 patients
- Extensive monitoring
- Safety and tolerability in patients
- Often complicated design, explorative, longer studies
- Selection of optimal dose
- Pharmacokinetics in patients
- Effect in special populations
- Explorative

Phase 3 trials



- 500-15000 patients
- Effect is verified in the target population
- Forms the basis of the NDA, New Drug Application
- Interactions between drugs start to become measurable in the larger population
- sub-groups start to be established
- special features and problems show up
- Confirmative
- Large, 6 mths to 3-5yrs

Phase IV trials



- Often large 500-15000 patients
- Further investigation of efficacy and safety post approval
- Special populations
- New indications
- Marketing

Planning of clinical trials- Line of sight

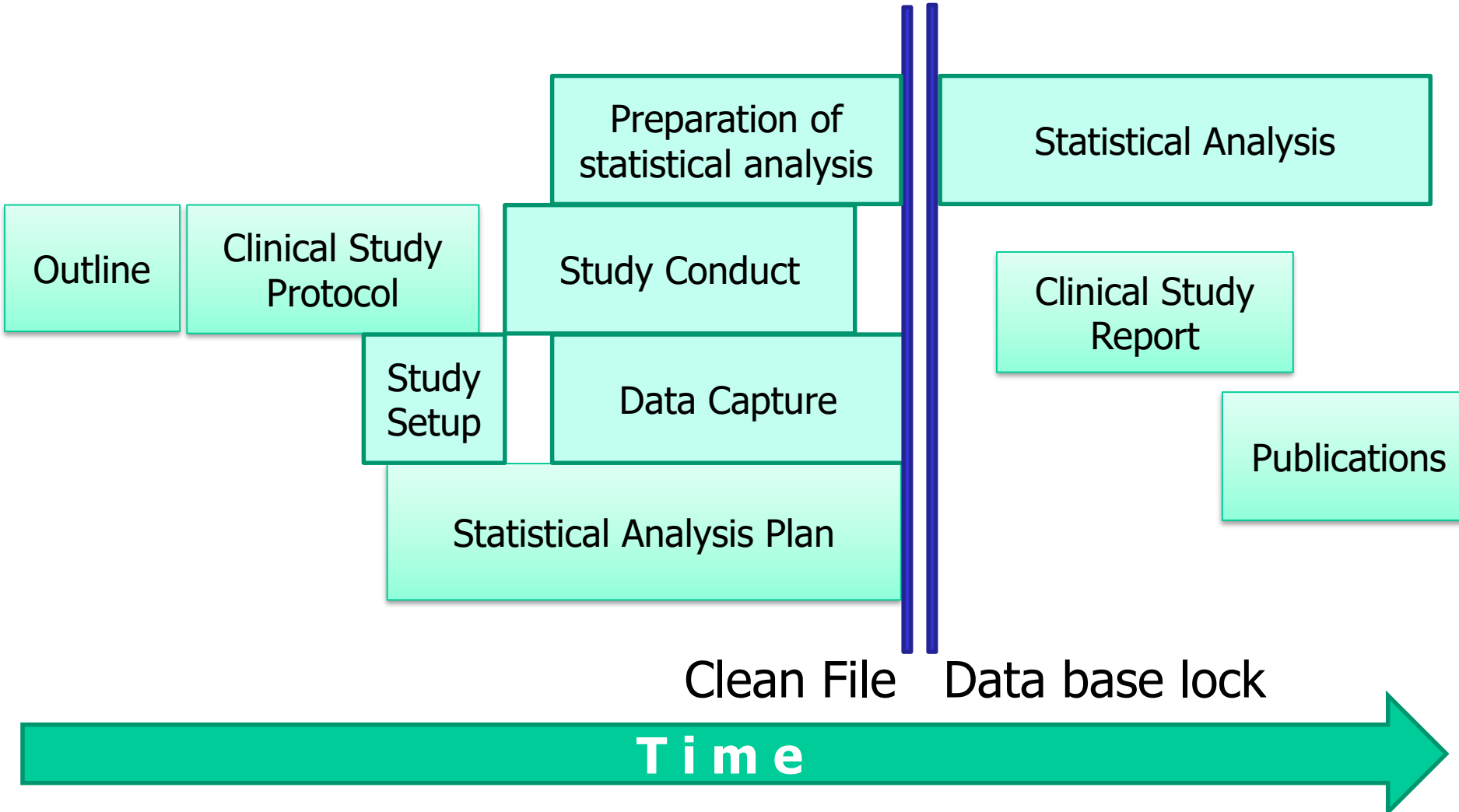
- Planning of Ph I:

Understanding of what to do in Ph II and III

- Planning of Ph II:

Understanding of what to do in Ph III

The Clinical Study Process



Good clinical practice (GCP)

- A set of standards for clinical studies to achieve and mantain high-quality clinical research in a sensible and responsible manner.
- Concerns patient protection and data quality.
- Need to standardize regulatory requirements -> creation of The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).

ICH
harmonisation for better health

Topics:

- Safety
- Efficacy
- Quality
- Multidisciplinary

ICH quality guidelines

Harmonisation achievements in the quality area include pivotal milestones such as:

- the conduct of stability studies
- defining relevant thresholds for impurities testing
- a more flexible approach to pharmaceutical quality based on Good Manufacturing Practice (GMP) risk management.

ICA safety guidelines

ICH has produced a comprehensive set of safety Guidelines to uncover potential risks like:

- carcinogenicity, genotoxicity and reprotoxicity
- A non-clinical testing strategy for assessing the QT interval prolongation liability, which is the single most important cause of drug withdrawals in recent years.

•S7A: Safety Pharmacology Studies for Human Pharmaceutical
•S7B: The Non-Clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT prolongation) by Human Pharmaceutical

ICH efficacy guidelines

- The work carried out by ICH under the Efficacy heading is concerned with:
- The design, conduct, safety and reporting of clinical trials
- Novel types of medicines derived from biotechnological processes
- The use of pharmacogenetics/genomics techniques to produce better targeted medicines.

ICH efficacy guidelines

- Clinical Safety E1-E2F
- Clinical Study Reports E3
- Dose Reponse Studies E4
- Ethnic Factors E5
- Good Clinical Practise E6
- **Clinical Trials E7-E11**
- Clincal Evaluation of a Therapeutic Category E12
- Clincal Evaluation E14
- Pharmacogenomics E15-E16
- Cross Cutting Topics E17

ICH efficacy guidelines

- E7: Studies in Support of Special Populations, Geriatrics
- E8: General Considerations for Clinical Trials
- **E9: Statistical Principles for Clincal Trials**
- E10: Choice of Control Group and Related Issues
- E11: Clinical Investigation of Medicinal Products in the Pediatric Population

Where to look for information

ICH (international Conference on Harmonisation)

FDA (Food and Drug Agency)

EMEA (European Medicines Agency)

Cochrane Collaboration

Chapter 1 Reading instructions

- 1.1 What are clinical trials: Read
- 1.2 History of clinical trials: Less important
- 1.3 Regulatory process and requirements: Read page 14
- 1.4 Investigational new drug application: Read page 17–20
- 1.5 New drug application: Less important
- 1.6 Clinical development plan and practise: Read
- 1.7 Aims and structure of this book: Skip