EURORDIS
Rare Diseases Europe

Fundació Doctor Robert
UAB

Introductory overview of medicines development process

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Contents

- What is medical research?
- Evidence-based medicine
- Life cycle of drug development

WHAT IS MEDICAL RESEARCH?

- How do we define medical research?
  - Studies that help us understand and define aspects and limits of health and disease
    - Frequency: incidence, prevalence
    - Diagnosis
    - Natural course
    - Mechanisms
    - Risk factors
    - Impact of intervention (treatment)

WHAT IS MEDICAL RESEARCH?

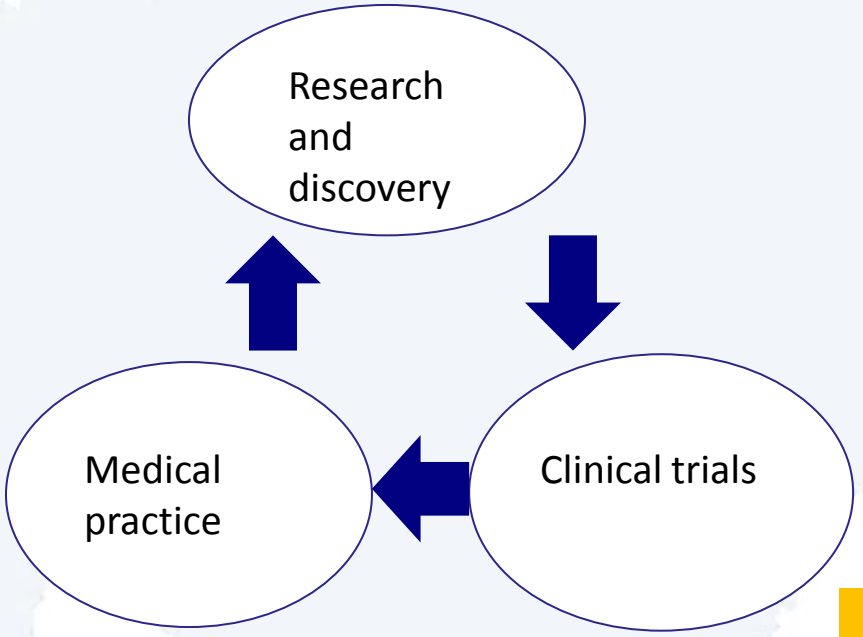
- Collecting and analysing data in a pre-planned, structured way – putting results in perspective with what we know
- Learning and confirming – developing hypotheses and testing them
- Non-clinical (”basic”) research:
  - ”In test tubes” (in vitro)
  - ”In life” (in vivo) in healthy animals or in animals with natural or induced disease

WHAT IS MEDICAL RESEARCH?

- Clinical research:
  - In healthy people
  - In people with suspected or confirmed disease or risk factors
- Must comply with ethics and legislation

TRANSLATIONAL RESEARCH

- Process ”from bench to bedside”
- Research in laboratory, in vitro, in vivo – discovery (R&D)
- Clinical trials
- Clinical practice



HOW IS MEDICAL RESEARCH DONE?

- Clinical research
  - Selected target population:
    - Criteria for study eligibility: Inclusion, exclusion
  - Observe only

  Or

  - Intervene (experiment)
  - Prospective, retrospective

HOW IS MEDICAL RESEARCH DONE?

- Epidemiological research
  - Population-based
  - Incidence and prevalence
  - Course of disease
  - Treatment
  - Observational – what happens without intervention?
  - Experimental – what is the effect of intervention, e.g. therapy?

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EVIDENCE-BASED MEDICINE (EBM)

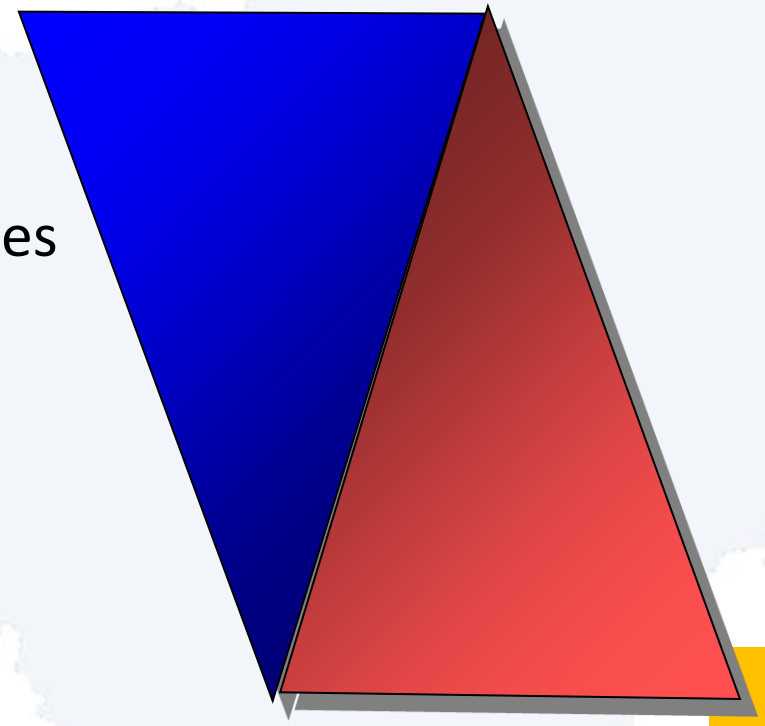
- "Old" concept – recognised for >100 years
- Care of individual patients is based on evidence
  - From medical research
  - From medical expertise and experience
  - Neither one alone is enough!
- Under constant refinement and change
- Who decides what is evidence and what is EBM?
- How do you judge what is good evidence and what is not?
- EU and International guidelines currently regulate EBM (see extra learning notes)

EVIDENCE-BASED MEDICINE

- Is it only a good thing?
- What has been criticised?
  - “Evidence-biased” medicine: only positive studies get published?
  - Refusal of certain therapies?
  - Limits freedom of patients and doctors – cookbook medicine
  - Serves health care cost-cutters

LEVELS OF EVIDENCE

- Meta-analyses of good quality randomised, controlled studies
- Individual randomised, controlled studies
- Meta-analyses of observational studies
- Individual observational studies
- Published case studies
- Anecdotal case studies
- Expert opinion



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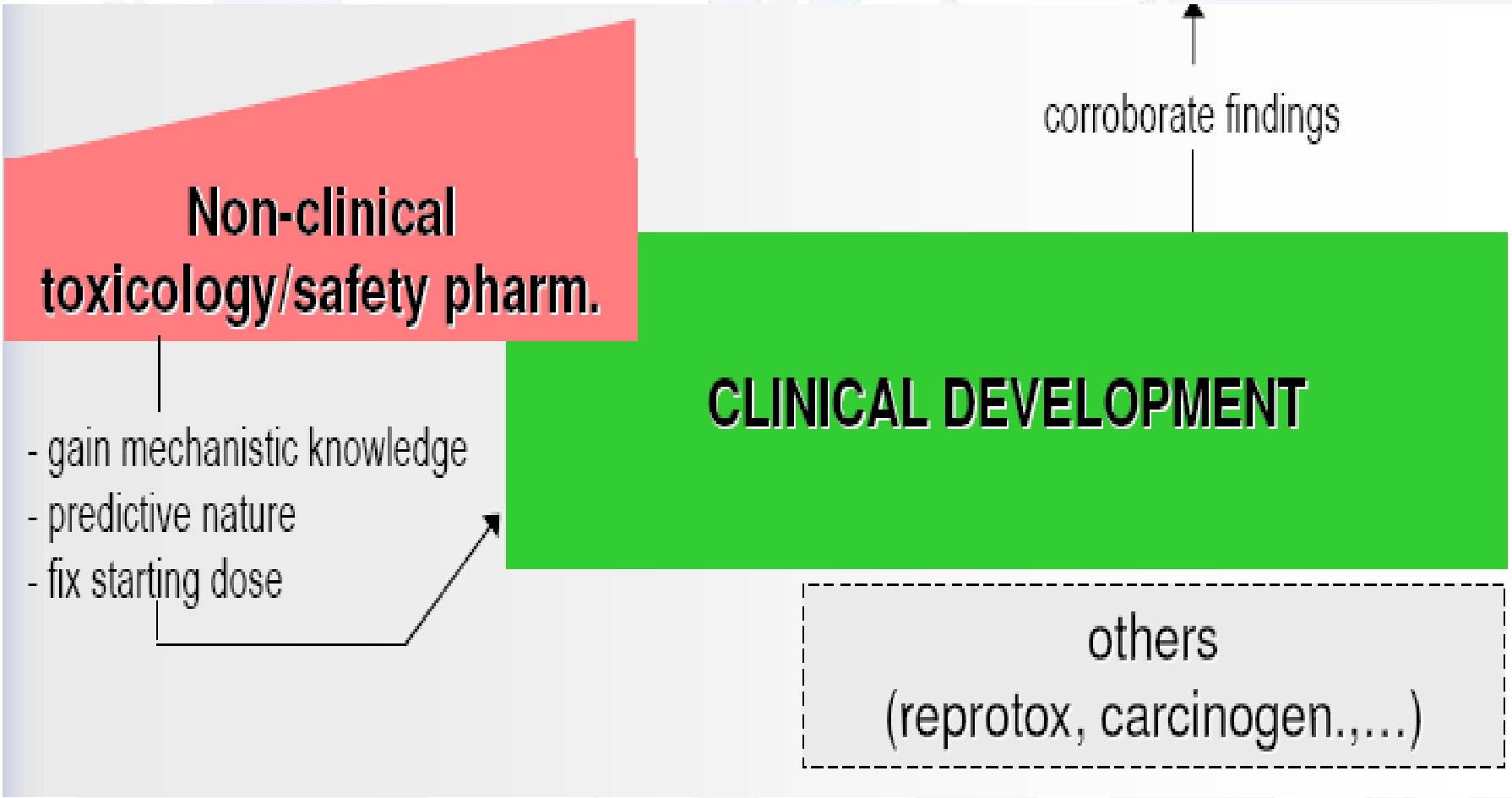
DEVELOPMENT STAGES



NON-CLINICAL (PRE-CLINICAL) DEVELOPMENT

- Certain non-clinical safety testing must be completed before new drug is given to humans
- Further testing must be completed before larger clinical trials
- Non-clinical and clinical studies are run partly in succession, partly in parallel

NON-CLINICAL DEVELOPMENT

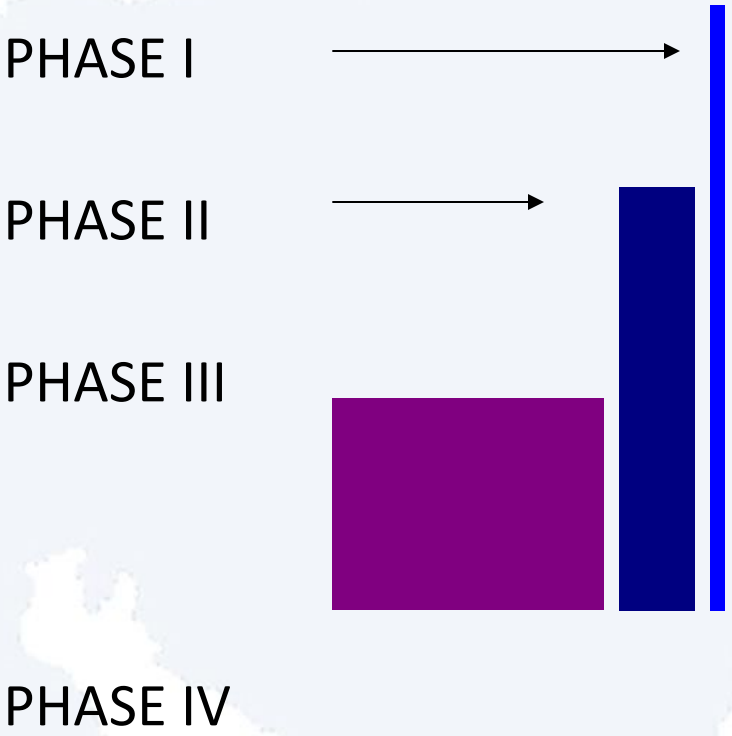
- Animal models of human disease available?
  - Non-clinical “proof-of-concept”
  - Naturally occurring diseases
  - Diseases occurring in certain animal strains
  - Diseases occurring in genetically modified strains

NON-CLINICAL DEVELOPMENT

- Toxicity – target organs
- Effects on heart, circulation, nervous system…
- Effects on fertility, foetal malformations
- Potential to cause mutations
- Potential to cause cancer

PHASES OF CLINICAL DEVELOPMENT

- Early clinical trials: learn!
  - Clinical pharmacology, Phase I
  - Therapeutic exploratory, Phase II
- Late clinical trials: confirm!
  - Main/pivotal/confirmatory studies, Phase III
- Post-authorisation
  - Safety and effectiveness in real life use, Phase IV



PHASE I

- First-in-man study
  - Safety, tolerability
  - Often in healthy volunteers
- Pharmacokinetics – ADME: how the drug is:
  - **A**bsorbed
  - **D**istributed in body
  - **M**etabolised
  - **E**xcreted
- How the drug interacts with other drugs and food
- Effect of age, kidney (renal) and liver (hepatic) disease, etc. on pharmacokinetics

PHASE II

- Early efficacy and safety studies in patients
  - Proof-of-concept: the drug shows expected effects, potential therapeutic benefit and acceptable safety
  - Finding the lowest effective and optimal dose (dose ranging studies)
  - Often in a “narrow”, stringently defined population
- Why is it often necessary to do early studies in a restricted population?
- If the drug was licensed based on early studies, what would that mean?

PHASE III

- Therapeutic confirmatory studies
  - Studies that provide confirmation of efficacy, safety and favourable balance of benefit and risk in the clinical target group
  - Ideally randomised, controlled study or studies
    - Study must have”internal validity” = freedom from bias
  - More permissive inclusion criteria
    - Study population should mirror ”real life” – ”external validity”

PHASE III

- Is one confirmatory study enough?
    - How much support is provided by earlier studies?
    - Is the effect plausible?
    - Study quality – how was the study planned and conducted?
- If a randomised, controlled study is not possible
    - Other designs – other levels of evidence?

PHASE IV

- Further efficacy/safety studies when the drug is in clinical use
  - Focus is on “according to approved label” use
  - Sometimes confirmatory evidence of efficacy and safety – in the context of conditional approval
  - Post-marketing safety when the drug is used according to approved label – Post Authorisation Safety Study (PASS)
  - Effectiveness in real life use
  - Referred to as post-marketing or post-authorisation studies

NEW THERAPEUTIC USES

"Off-label" use – new phase II-III studies

- Use in subgroups not covered by initial studies
- Studies that target new therapeutic indications
- New target groups (e.g. children, early disease, etc.)

TIME AND COST

- Typically:
  - More than 10 years from innovation and early non-clinical studies to confirmatory clinical trials
  - More than $100 million
- Early development by independent investigators/small company – final development by large company
- Early development by pharmaceutical company – project discarded – taken up by orphan drug development sponsor
  - Can be a patient advocacy group or foundation
- Whole development by one company
- Contract research organisation (CRO) involvement

Extra learning notes

EVIDENCE-BASED MEDICINE AND NEW DRUG LICENSING

- Directive 2001/83/EC of the European Parliament and of the Council on the Community Code relating to medicinal products for human use
  - The clinical particulars must enable a sufficiently well-founded and scientifically valid opinion to be formed
  - Clinical trials must always be preceded by adequate pharmacological and toxicological tests in animals
  - All phases of clinical investigation shall be designed, implemented and reported in accordance with good clinical practice

EVIDENCE-BASED MEDICINE AND NEW DRUG LICENSING

- Directive 2001/83/EC
  - All clinical trials shall be conducted in accordance with ethical principles – Declaration of Helsinki
  - In general, clinical trials shall be done as controlled clinical trials and if possible, randomised
  - The treatment of the control groups will vary from case to case
  - In some cases, it may be more pertinent to compare with an established medicinal product than with placebo

EVIDENCE-BASED MEDICINE AND NEW DRUG LICENSING

- International Conference on Harmonisation (ICH), Committee for Human Medicinal Products (CHMP) and Committee for Advanced Therapies (CAT) guidelines and reflection papers
  - General guidelines
  - Quality, efficacy and safety
  - Therapeutic area and disease-specific guidelines
  - Define expectations and requirements
  - Not binding – must be justified by company/sponsor if not followed