Drug Discovery and Development

How are drugs discovered and developed?

Sources of drugs

Animal - **insulin** (pig, cow)
- **growth hormone** (man)

Plant - **digitalis** (digitalis purpurea-foxglove)
- **morphine** (papaver somniferum)

Inorganic - **lithium**

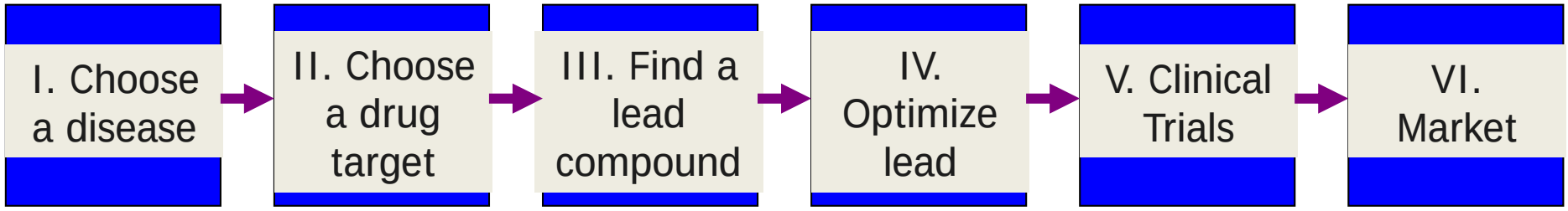
Synthetic - **chemical** (propranolol)
biological (penicillin)
biotechnology (human insulin)

How a new drug development proceeds?

- Idea or Hypothesis
- Design and synthesis of substances
- Studies on tissues and whole animals (preclinical studies)
- Studies in man (clinical studies)
- Grant of an official license to make therapeutic claims and to sell
- Post-licensing (marketing)studies of safety and comparisons with other medicines.

Drug Discovery

- General plan:



For a New Chemical Entity (NCE)

- More than 10 years
- More than $500 million
- More than 10000 tested compounds
- For one drug!

Basic Steps

- Choose a disease
- Choose a drug target
- Do a “bioassay”

  bioassay = A test used to determine biological activity.
- Find a “lead compound”

  “lead compound” = structure that has some activity against the chosen target, but not yet good enough to be the drug itself.
- If not known, determine the structure of the “lead compound”
- Synthesize analogs of the lead
- Identify Structure-Activity-Relationships (SAR’s)

Choosing a Disease

- Pharmaceutical companies must make a profit to exist
- Pharmaceutical companies will, therefore, avoid products with too small a market (i.e. a disease which only affects a small subset of the population)

Choosing a Disease

- Pharmaceutical companies will also avoid products that would be consumed by individuals of lower economic status (i.e. a disease which only affects third world countries)
- Most research is carried out on diseases which afflict “first world” countries: (e.g. cancer, cardiovascular diseases, depression, diabetes, flu, migraine, obesity).

Choosing the Bioassay

In vitro testing

- Has advantages in terms of speed and requires relatively small amounts of compound.
- Speed may be increased to the point where it is possible to analyze several hundred compounds in a single day (high throughput screening).
- Results may not translate to living animals

In vivo tests

- More expensive
- May cause suffering to animals
- Results may be clouded by interference with other biological systems

TECHNIQUES OF DISCOVERY

- **MOLECULAR MODELLING** – AIDED BY THREE DIMENTIONAL COMPUTER GRAPHICS ;
- ALLOWS THE DESIGN OF STRUCTURES BASED ON NEW AND KNOWN MOLECULES TO ENHANCE THEIR DESIRED & TO ELIMINATE THEIR UNDESIRED PROPERTIES TO CREATE HIGHLY SELECTIVE TARGETED COMPOUNDS.

- **COMBINATORIAL CHEMISTRY** –RANDOM MIXING AND MATCHING OF LARGE NUMBERS OF CHEMICAL BUILDING BLOCKS TO PRODUCE LIBRARIES OF ALL POSSIBLE COMBINATIONS .
- GENERATES BILLIONS OF COMPOUNDS , SCREENED BY HIGH- THROUGHPUT SCREENING(THOUSANDS A DAY) . IF POSITIVE RESPONSE, TRADITIONAL LABORATORY METHODS .
- **BIOTECHNOLOGY**- PROTEINS AS DRUGS , USE OF RECOMBINANT DNA TECHNOLOGY / GENETIC ENGINEERING TO CLONE AND EXPRESS HUMAN GENES .

Preclinical Studies in animals

- **Pharmacodynamics**: To explore actions relevant to the proposed therapeutic use
- **Pharmacokinetics**: how the drug is distributed in and disposed of by the body
- **Toxicology** : whether and how drug causes injury (in vitro tests and intact animals)

-- **single-dose studies - acute toxicity**

-- **repeated dose studies – sub-acute**

chronic or long term toxicity

--- Done in 2 species – rodent and non-rodent

--- Clearance from Institutional Animal Ethic Committee required

Special toxicity study

- Carcinogenecity
- Teratogenecity
- Mutagenecity
- Local toxicity –dermal, ocular, inhalational, vaginal & rectal
- Effect on reproductive performance

R R R

Reducing animal usage

- **REPLACEMENT**: use non-animal tests if possible (cheaper, less trouble, less variable but not possible for everything at this time)
- **REDUCTION**: get the statistics right, don't replicate work unnecessarily, don't over-breed
- **REFINEMENT**: reduce suffering and severity of procedure, pay attention to housing, stress, husbandry and rich environments, proper analgesia and pre- and post- operative care .
- According to Good Laboratory Practice (GCP)

Rational Introduction Of a new drug to man

- When studies in animals predict that a new molecule may be a useful medicine i.e. effective and safe in relation to its benefits, then time has come to put it to test in man.

Clinical testing(trials)

- **Phase I** – Human Pharmacology (Healthy volunteers – 20-50 subjects)
- **Phase II** - Therapeutic Exploration (patients – 50- 400)
- **Phase III** – Therapeutic Confirmation (large scale multi-centre; 250-1000)
- **Phase IV -** Therapeutic Use (post-registration monitoring)

{Phase 0 , Microdosing}

Clinical Trials

- **Phase I** : Drug is tested on healthy volunteers ,
- P/K , P/D (biological effects) ,tolerability, safety, efficacy.
- To determine safe clinical dose range.
- If drug is expected to have significant toxicity, volunteers with that disease are taken rather than healthy volunteers, (anti-cancer, drugs for AIDS)
- These trials are **non-blind** or **open-label**; both the investigator and the subject know what is being given.

- **Phase II :**
- Drug is tested on small group of **patients with the target disease.**
- P/K , P/D , dose range, safety and efficacy may involve comparison with a control.

- **Phase III**: Drug is tested on much larger group of patients and compared with existing treatments and with an inert control. These are randomised double-blind trials.
- Takes 5-6 years for completion.
- Results analysed statistically in the end.

- **Phase IV** :
- Drug is placed on the market and patients are monitored for side effects
- Post –marketing surveillance for safety, efficacy & pharmaco-economic studies.

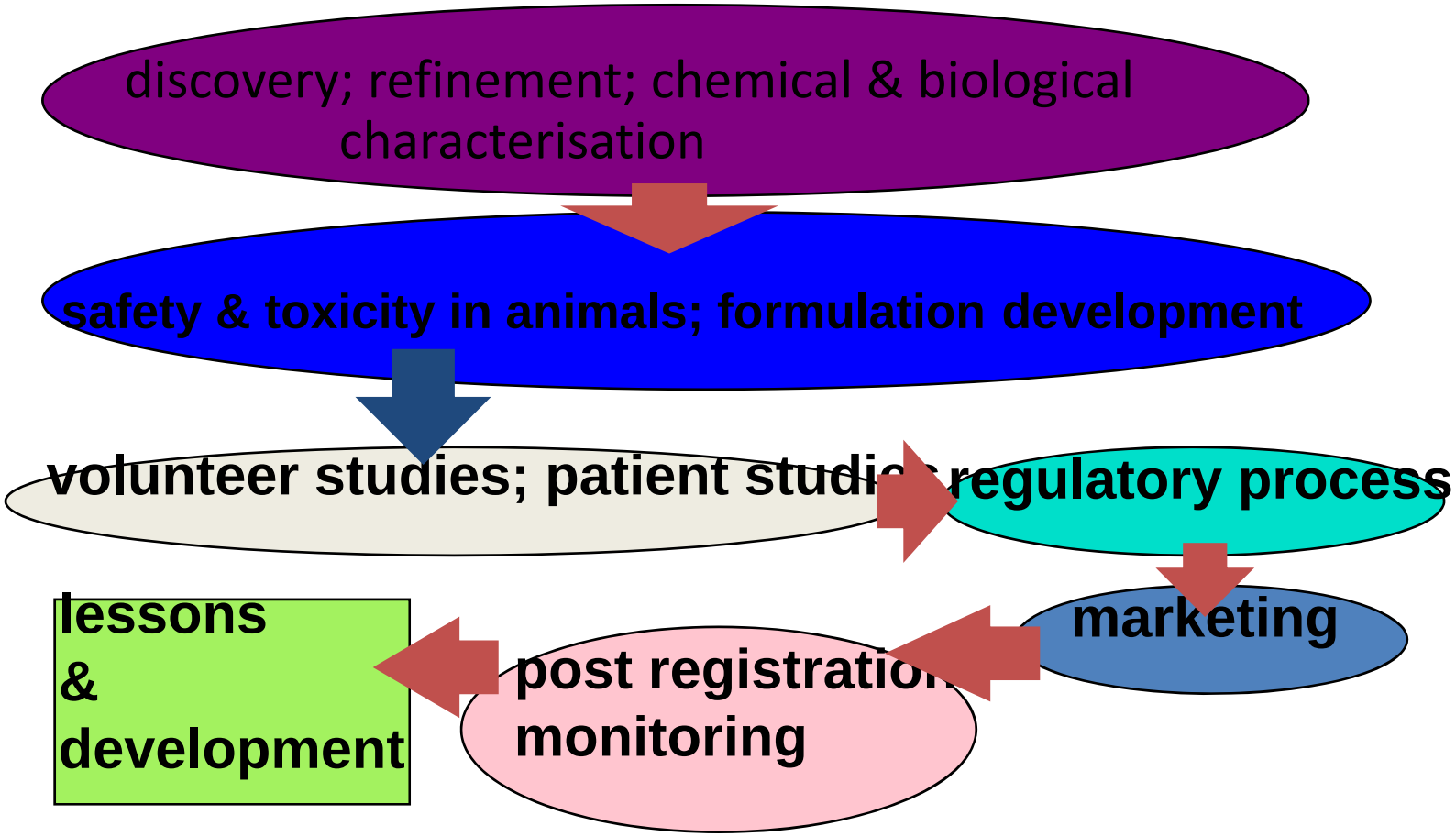
Drug Regulation

- **Food & Drug Administration (FDA)**
- It is the administrative body that oversees the drug evaluation process in USA and grants approval for marketing of new drug products.
- **IND** - Investigational New Drug (if judged ready to be studied in human)
- **NDA** - New Drug Application
- If Phase 3 results meet expectations , application is made for permission to market the new agent)
- Filing of a patent

Ethics Of research in Human

- Ethical Principles of research –
- **Autonomy** – Right to self determination, **informed consent**
- **Beneficence** – Desire to help patients
- **Non-maleficence** – No harm
- **Justice** – should not be continued if no benefit

Drug discovery/development process



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