Drug development

Introduction

Drug development is an expensive ($800m) and time-consuming (~10 years lab → market) process in which most (99%) candidates fail, culminating in a costly patented product.

Potential returns

- Extraordinary >$400m/year e.g. omeprazole
- Successful $200-400m/year e.g. seretide
- Viable <$200m/year e.g. IFN-a

Global market: $35b

Therapeutic need

Determined by

- Existing therapies
  - Well-served diseases: cardiovascular, asthma (but room for improvement)
  - Poorly-served diseases: chronic neuro diseases
  - Major opportunities: HIV/type I DM vaccines
- Commercial potential
- Patient/public demands
- Individualisation of treatment (genomics)

Phases of drug development

Drug development is conventionally divided into preclinical and clinical, and the latter into 4 phases. At the end of each phase, the data on any development compound is reviewed and decisions to continue or abandon development are made. Such an approach is taken to maximise patient safety and minimise expenditure (the reasons for terminating R&D are roughly equally split between safety, efficacy and economics). The cost of development is not evenly distributed but increases exponentially from phase 1 to phase 3.

Pre-clinical (*in vitro*)

- Target identification
- Hit identification
  - Develop assay system
  - Screen library for active compounds (robotical; high/ultra-high throughput)
- Lead identification (isolate active chemical entity)
  - Chromatography
  - Spectroscopy
  - X-ray crystallography
- Lead optimisation
  - Bioinformatics (e.g. solubility, absorption, QSAR – quantitative structure-activity relationship)
  - Potency, selectivity
  - ADME: absorption, distribution, metabolism, excretion
  - Formulation/marketing

Pre-clinical (*in vivo;* animals)

- Also involved in development of the chemical entity
- Proof of efficacy in animal models if available
- Toxicology assessment to support human dosing
  - Acute: ↑dose until 50% mortality
  - Chronic: reproduction, development, carcinogenesis
- Repeat dosing in two species (usually rodent and non-rodent, i.e. dog)

Clinical (*in vivo;* humans)

Phase I (clinical pharmacology)

- n=10s, volunteers
- Determine kinetics/food interactions/tolerability (single blind placebo; usually start with 1/10 to 1/100 of no effect dose in animal toxicology, adjusted for body mass)
- Dose-ranging

Phase II (early efficacy data)

- n=100s, patients
- Phase 2a
    - Surrogate markers of efficacy[1]
- Phase 2b
    - Efficacy in disease

Phase III (pivotal efficacy studies)

- n=1000s
- Usually 2 large RCTs vs. placebo/best alternative Rx
    - Demonstrate safety and efficacy for registration
    - Monitor surrogate and primary markers

Phase IV (post marketing)

- New formulations, new indications, less SEs
- Pharmacoecomonic assessment (e.g. NICE)

Note

- Cannot use this approach for e.g. cytotoxics, where administration to volunteers would be unethical
- Sometimes fails to prevent harm, e.g. thalidomide

Responsibility for safety

Ultimately, responsibility for safety lies with the pharmaceutical company, and is in their best commercial interest:

- Increasing cost throughout development
- Late withdrawals (e.g. Lipobay®/cerivastatin) are costly and damage the company's image
- As do dangerous drugs that make it onto the market

However, regulations are enforced by independent bodies each step along the way:

- Pre-clinical: animal protection legislation
- Clinical
    - 'Good Clinical Practice' code of conduct applies to research doctors, too
    - Ethics Committee (professional and lay people; approve study design, questionnaires, adverts, info sheets…)
    - Registration: before a new drug can be approved for prescribing, regulatory authorities must review all data (preclinical and clinical) to ensure effectiveness and safety
        - UK: MCA (Medicines Control Agency), being integrated into…
        - EU: EMEA (European Medicines Evaluation Agency)
        - US: FDA (Food and Drug Administration)
        - IHCs attempt international harmonisation

        - Usually consulted at all stages of the new drug's development to ensure that unforeseen gaps in the clinical development do not arise.

Influence of DNA sequence data

Human genome project → many grandiose predictions – born out to what extent?

[1] Biological measurement that substitutes for therapeutic end-point; requirements: easy to measure, reproducible, high sensitivity/specificity, dose-response, acceptable – e.g. CD4 count in HIV

Development process

Traditional (e.g. morphine)

- *In vivo*
- Trial-and-error

Empirical (e.g. β-blockers)

- *In vivo*
- Some understanding of pathophysiology

Molecular

- *In vitro*
- Designing a ligand for a known structure
- Categories
    - Rational drug design (e.g. captopril)
    - Random screening (pragmatic, currently dominant)
    - Anti-sense approach
- Now exploiting fruits of Human Genome Project by developing drugs blocking putative R although function and natural ligands unknown, hoping that they will be useful once the physiology is better understood
- Lead optimisation of structure-affinity relationship (max. affinity for R, min. affinity for other R)
- High throughput due to new technology
    - Molecular biology
    - Instrumentation/robotics
    - IT
- Candidate selection

- *In silico* in the future?

New types of drug

Anti-sense drugs
Gene therapy

Pharmacogenetics

In addition to diagnostic/prognostic disease genetics

Predict response (benefits/SEs) of individual patient by predicting absorption/distribution/elimination/receptor morphology

→ allows for disease heterogeneity (e.g. DM, AD)
→ need not prove cost-effectiveness in broad population

Already possible, e.g.

- Isoniazid-induced neuropathy in slow acetylators
- Pravastatin and homozygosity for B_1 allele of cholesterol ester transfer protein

Gene therapy

Potential dangers

Human manipulation of own germ line

- Individual: dangers of manipulating a poorly understood system
- Population: genetic alterations are transmitted vertically, and become uncontrollable once ‘in the wild’
- Global: already an overpopulated planet…

Formularies

= listing of drugs comprehensive enough in range and information provided to enable health practitioners to prescribe appropriate treatment

Types

- National: BNF
- Hospital/GP
- Speciality
- Personal

Rationale

- Informed, safe prescribing
- Economic influences (NICE; can still get on named-pt. basis after independent check)
- Local disease prevalence
- Local drug availability