Development of a new medicinal product

as. MUDr. Martin Votava, PhD.
Development and registration of a medicinal product

Costs of development: 800 mil USD

Time to develop: 10 years

Successfulness: 0,005% - 0,001%
Development of a new medicinal product

- Chemical synthesis and development of pharmaceutical form
- Preclinical models
- Development of methods
- Preclinical PK and PD
- IND
  - Dose Escalation a iniciální PK
  - „Proof of Concept“ a „Dose Finding“
- N=10-100
- N=100-1000
- N>1000

Phase I
- PK/PD studie u speciálních populací

Phase II
- Velké studie účinnosti

Phase III
- Clinical development

Preclinical development

NDA
Choice of chemical entity (n=10000)
New chemical entity

• modification of chemical structure of a known medicinal product
• use of natural compounds
• use of new features of known active substances
• drug design – targeted synthesis of new chemical entities
Preclinical development
(n = 100-1000)
Aims of preclinical development

• To identify potential adverse drug reactions
  – Target toxicity organs
  – Reversibility of changes

• PK profile

• PD effect
  – „Proof of Principle“

• To establish safety administration in humans
  – Safe and effective starting dose in humans
  – To establish main monitoring parameters during clinical studies
Preclinical safety studies

- Safety pharmacology
- Toxicokinetics & pharmacokinetics
- Acute toxicity
- Chronic toxicity
- Special toxicity studies
  - Carcinogenicity
  - Mutagenicity
  - Genotoxicity
  - Phototoxicity
  - Local tolerance
  - Reproductive toxicity
  - Oculotoxicity etc...
Safety pharmacology

• Influence of the drug on the specific organ systems
  – Cardiovascular (QT interval…)
  – CNS (convulsion, sedation atd.)
  – Respiratory system

• Results before first administration to human
Toxicokinetics & pharmacokinetics

• Analytical method
• Preclinical PK/PD efficacy and safety
• Testing of pharmaceutical form
• Testing of different doses and dosing schedules
• ADME in different species
Preclinical toxicity

• GLP studies
• Use of intended dosing schedule, pharmaceutical form
• Studies of acute toxicity in two mammals species before the first administration in human
  – Rats and dogs for small molecules
  – Primates for biologicals
• Studies of chronic toxicity requirements
  – 3-months for administration < 3 months in humans
  – 6-months for administration > 6 months in humans
Special toxicity studies

- Carcinogenicity
- Mutagenicity
- Genotoxicity
- Phototoxicity
- Local tolerance
- Reproductive toxicity
- Oculotoxicity etc...
Clinical trials
(n = 10 - 100)
Clinical trial

any systematic evaluation of a drug effect in humans for the purpose:

– 1. to evaluate clinical pharmacological or any other pharmacodynamic properties
– 2. to evaluate adverse reactions
– 3. to evaluate pharmacokinetic parameters
Good clinical practice

• Good clinical practice is a set of internationally recognised ethical and scientific quality requirements which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects.

Directive 2001/20/EC
Clinical trials

**Phase I** trials are the first stage of testing in human subjects.

**Phase II** trials are designed to confirm „proof of principle“ concept in the target groups of patients
- Phase IIA is specifically designed to assess dosing requirements
- Phase IIB is specifically designed to study efficacy

**Phase III** trials are large confirmatory clinical trials, basis for marketing authorization of a drug

**Phase IV** - Post Marketing Surveillance Trials
Clinical studies

• Controlled
• Randomised
• Blinded
• Multicentre

• GCP, Informed consent
Research activities in CZ

- Basic research
- Pharmaceutical development
- Preclinical tests
- Clinical studies
- Postmarketing studies

- No commercial research centers
Life-cycle of a medicinal product

- Patent protection
- Market access of a generic product
- Application for marketing authorization of a generic product
- Price and reimbursement
- Patent registration
- Marketing authorization
- Data exclusivity

Research and development
Marketing authorization (n = 1)
Marketing authorization

• National
• Mutual recognition procedure
• Decentralised procedure
• Centralised procedure
Prices and reimbursement (n=0 ?)
Prices and reimbursement

- Efficacy
- Effectiveness
- Efficiency

- Public interest
- Cost-effectiveness

- Innovative therapy
- Therapeutic guidelines
- Impact of health outcomes

- Price for QALY
Patent protection of medicinal products
Patent law

• Different in every state
• Applies not only for new chemical substances, but also for:
  – chemical process
  – pharmaceutical form
  – new use of old molecules
  – manufacturing steps
  – etc...
Evropean patent

- based on one application form to EPO

- But not valid for the whole EU area, but its multiple national patent

- need of validation in each member state $\rightarrow$ translations $\rightarrow$ relatively high costs
Questions??