Development of a new medicinal product

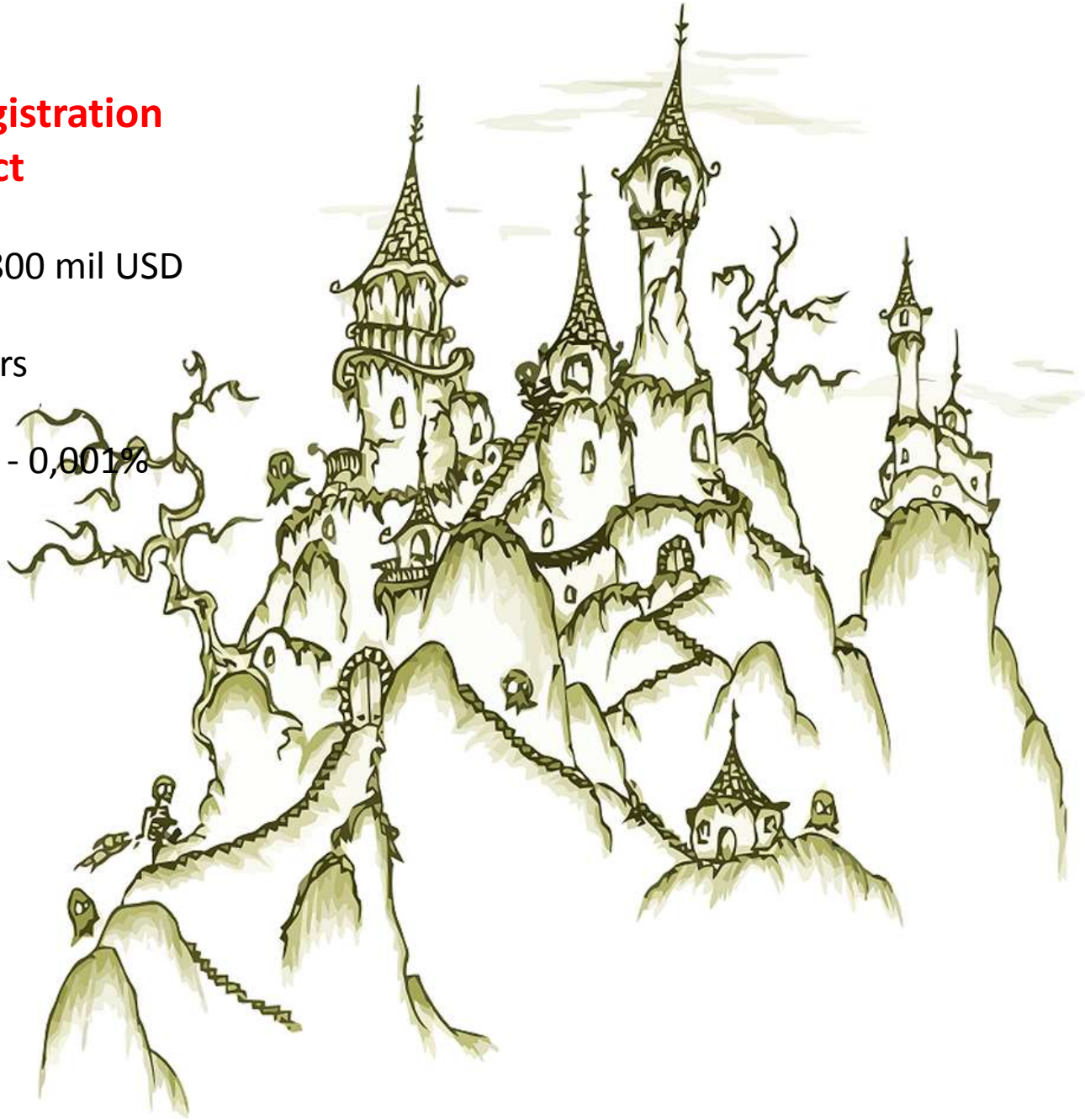
as. MUDr. Martin Votava, PhD.

Development and registration of a medicinal product

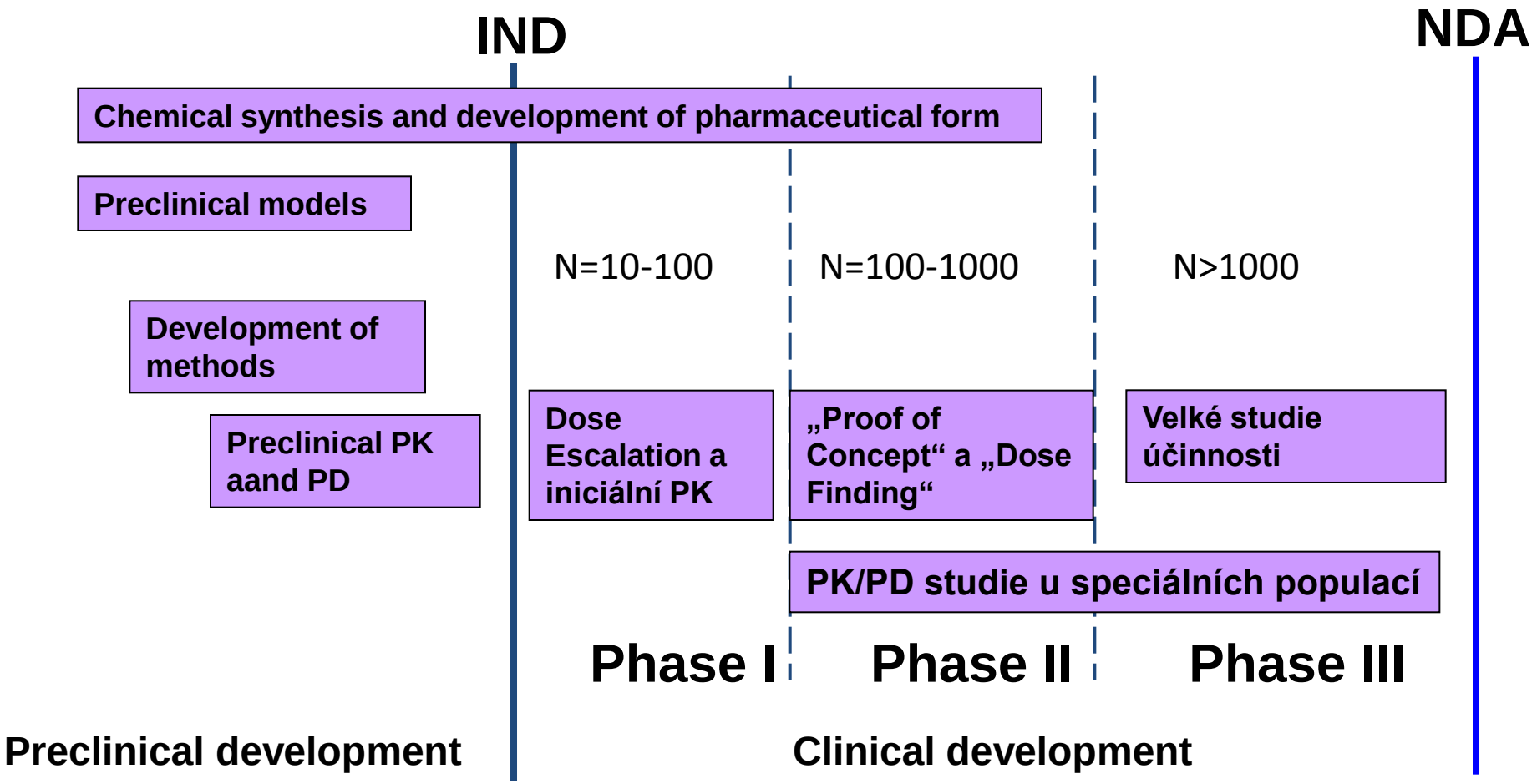
Costs of development: 800 mil USD

Time to develop: 10 years

Successfulness: 0,005% - 0,001%



Development of a new medicinal product

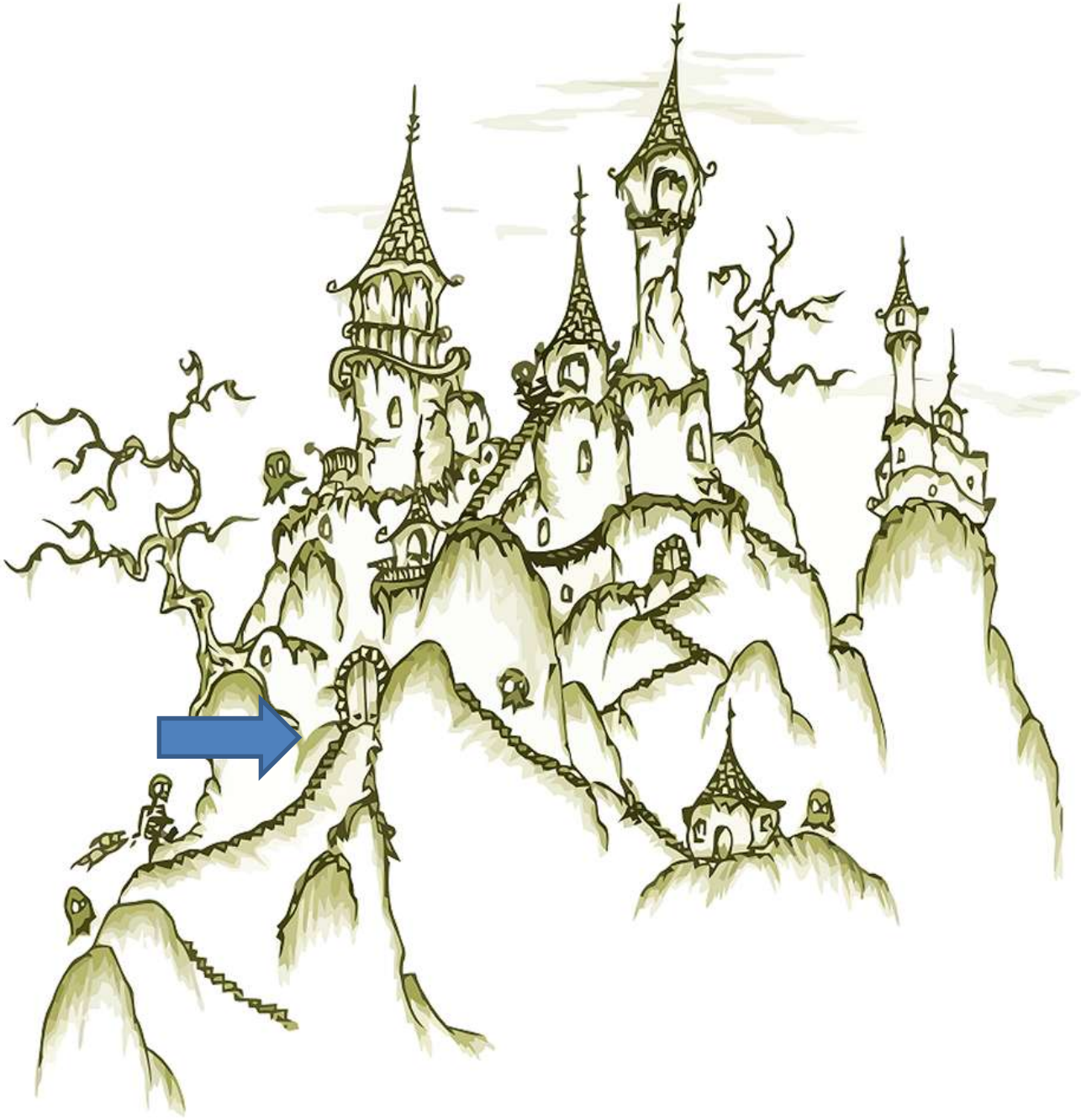


Choice of chemical entity (n=10000)

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 moleculs
  - Primates for biologicals
- Studies of chronic toxicity requirements
  - 3-months for administartion < 3 months in humans
  - 6-months for administartion > 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

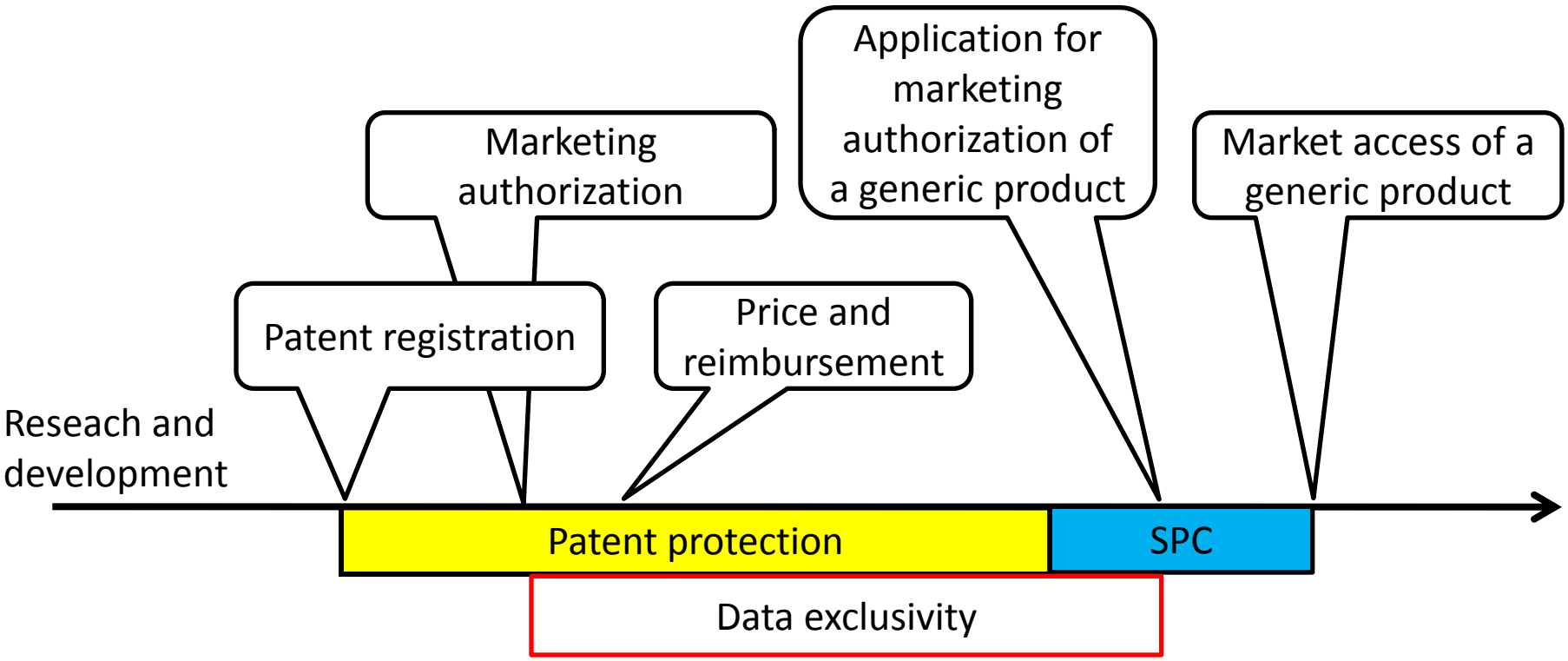
- GCP, Informed consent

Research activities in CZ

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

- No commercial research centers

Life-cycle of a medicinal product

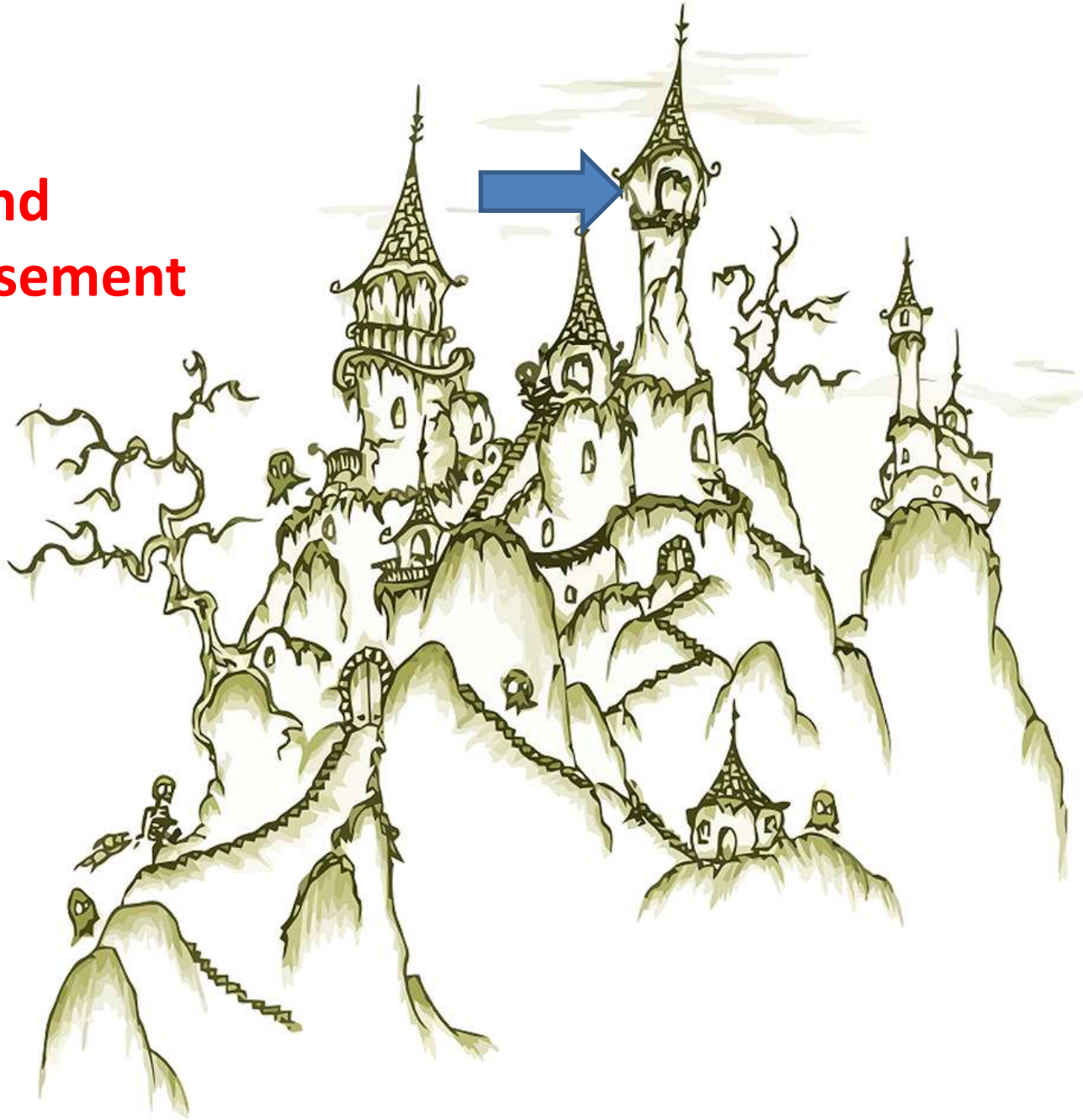


Marketing authorization (n = 1)

Marketing authorization

- National
- Mutual recognition procedure
- Decentralised procedure
- Centralised procedure

Prices and reimbursement (n=0 ?)



Prices and reimbursement

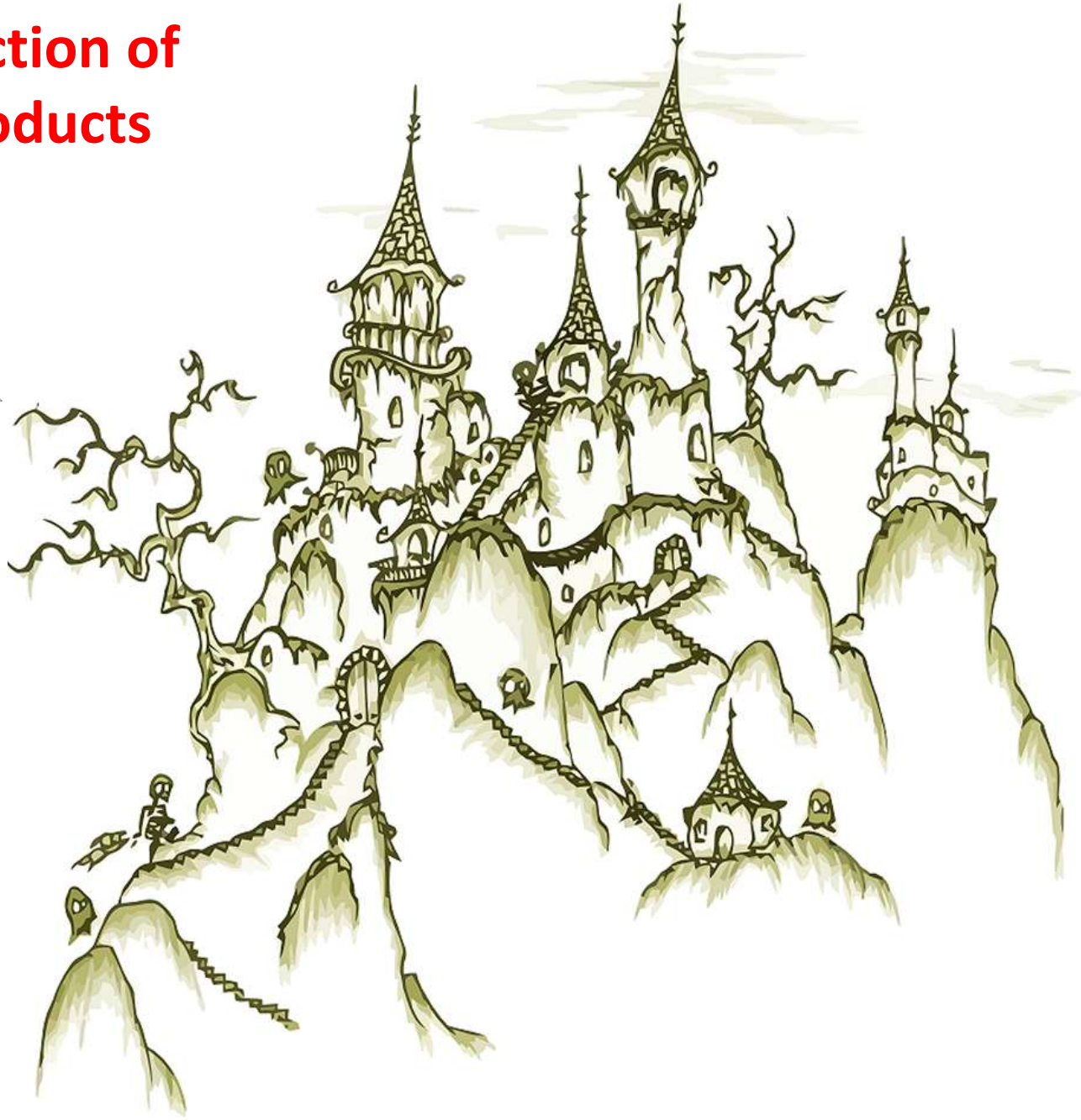
- Efficacy
- Effectiveness
- Efficiency

- 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 → translations → **relatively high costs**

Questions??