Pharmaceutical Biotechnology 2024

Lecture 14

Chapter 6.1. REGULATORY ISSUES in Pharmaceutical Biotechnology

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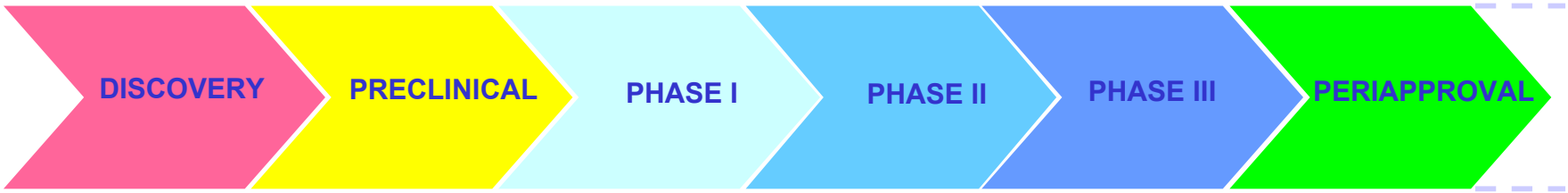
The Development Process –by Decision Points



> 100‘000 real / virtual NMEs

> 40 NMEs leads

> 20 candidates

> 10 clincially tested

> 1.5 products

- Discovery
- Proof of Concept
- Commerzialization

NME – New Molecular Entity

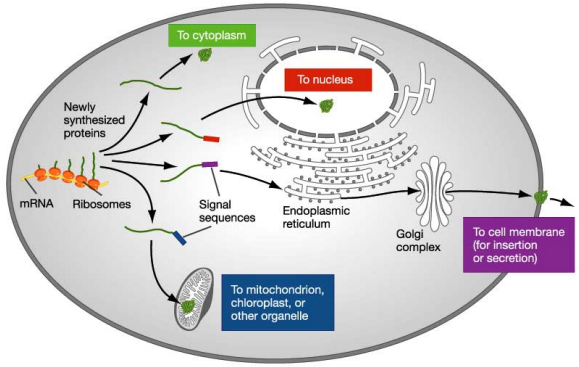
The Development Process

Standardized production -

challenge of biotechnologic - derived medicinal products

Synthetic versus biotechnology-derived Medicinal Products – the difference

Difference in complexity



Synthetic versus biotechnology-derived Medicinal Products – the difference

„The process makes the product“

Any change in the production may change the product

Any change in the product may change the efficacy and safety

Product Development

Which Product?

Manufacturing - synthetic versus biotech

Formulation – transport vehicle to the target

Packaging – a tricky challenge

Which product?

Major questions to be asked

- Which are the potential indication?
- What is the suitable application route?
- Which administration forms are possible with the active principle?

Preclinical Development

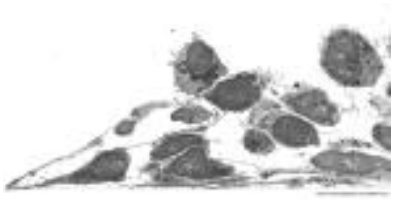
What is the purpose of preclinical development?
What has to be avoided by all means?

Preclinical Development – Cautious approach

Botulinum toxin (Clostridium botulinum)
Human lethal dose:
1.3–2.1 ng/kg intravenously or Intramuscularly
(10–13 ng/kg when inhaled).

Curare (plant derived alkaloid):
Human lethal dose, **375 µg kg^{-1}** (injected)

Preclinical Development – Cautious approach



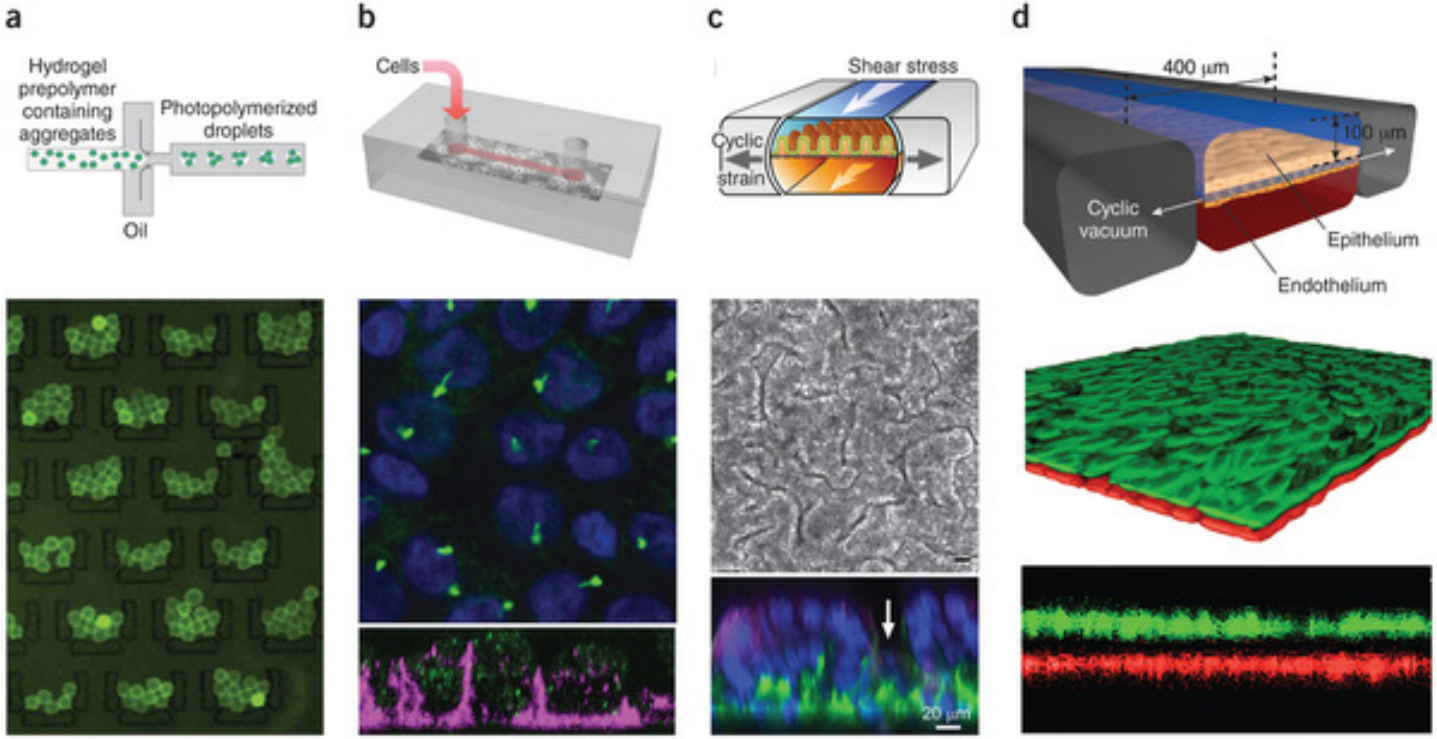
- In-silico
- In-vitro
- Ex-vivo
- Animal models

Microfluidic organs-on-chips

- For preclinical studies
- *Nature Biotechnology* **32**, 760–772 (2014)

Micro-tissues in hydrogels

- (a) liver-on-a-chip
- (b) kidney-on-a-chip
- (c) gut-on-a-chip
- (d) lung-on-a-chip



Preclinical Development – Cautious approach

Toxicology

- Acute
- Sub-Chronich
- Chronich

Preclinical Development – Cautious approach

Answers from Preclinical Testing

Minimal toxic dose

Minimal therapeutic concentration

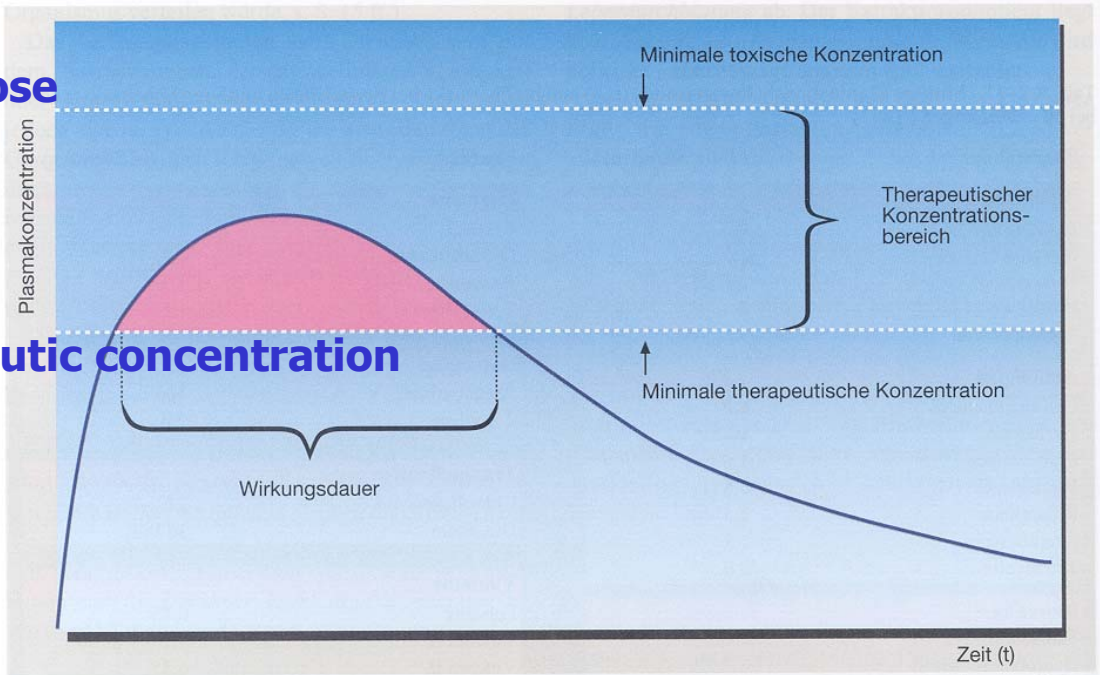


Abb. A 2–18. Ermittlung des therapeutischen Konzentrationsbereichs durch Bestimmung der minimalen therapeutischen und der minimalen toxischen Wirkstoffkonzentration

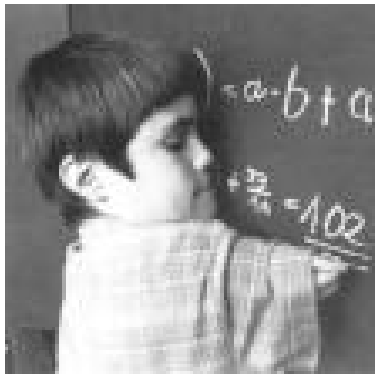
Preclinical Development – Cautious approach

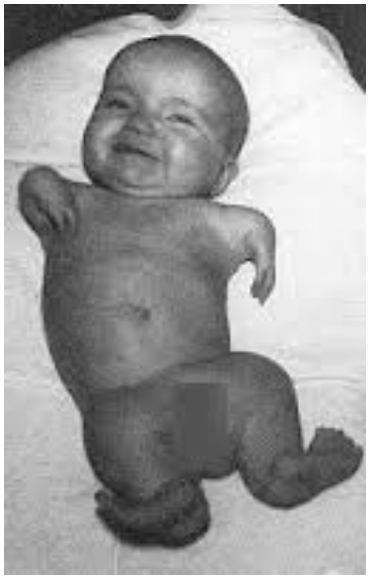
Reproduction

Preclinical Development – Cautious approach

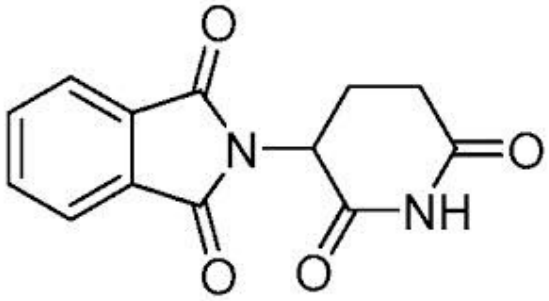
Teratogenicity

Contergan = Thalidomide
Germany: 1961/62





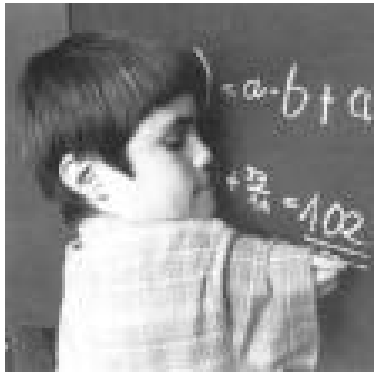
Thalidomide



Preclinical Development – Cautious approach

Teratogenicity

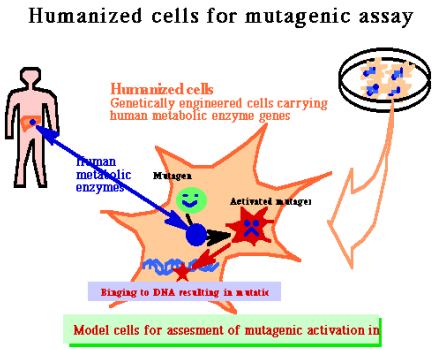
A teratogen is an agent that can disturb the development of an embryo or fetus. Teratogens may cause malformation of organs or parts of the body.



Thalidomide

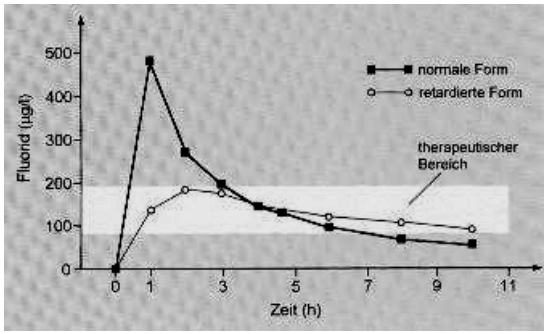
Preclinical Development – Cautious approach

Mutagenicity



Preclinical Development – Cautious approach

Pharmacokinetics



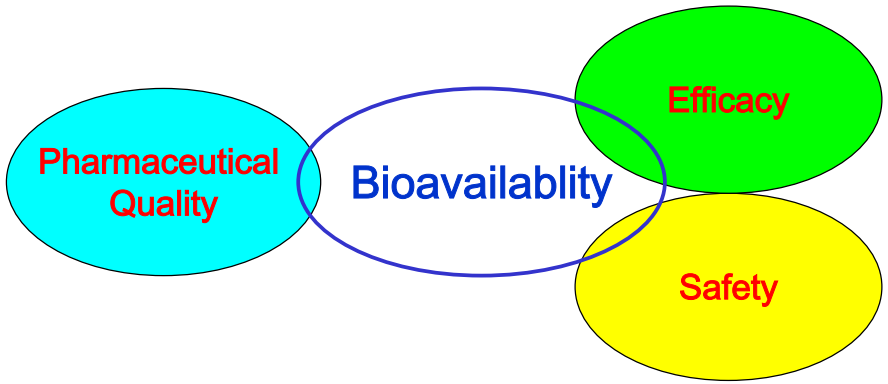
Preclinical studies

- Preclinical trials involve cell culture and animal studies, not studies in human. The main purpose of preclinical trials is to test the **biosafety** of a product before it is applied for clinical studies.
- **Main Parameters, which are tested:**
- Toxicity (acute, sub-chronic, chronic) + Special toxicity studies (Mutagenicity, Teratogenicity, Developmental- and Reproductive Toxicity, Neurotoxicity, Cardiotoxicity, Immunotoxicity)
- Pharmacodynamics (Mechanism of action, dose response relationship)
- Pharmacokinetics (Absorption, Distribution, Metabolism, Excretion, Plasma half-life)

Clinical Development

Bioavailability
First in man
Which dosage / regimen?
Design

Bioavalability



First Steps in Man Phase I

Question 1:

How does the body process a new drug?

- **A**bsoprtion
- **D**istribution
- **M**etabolism
- **E**xcretion

→ **Kinetic properties**

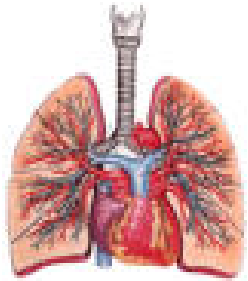
- Time course of drug concentration
- Interface between dose and concentration

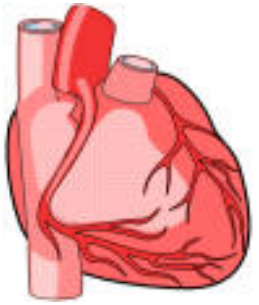
→ **Bioavailability**

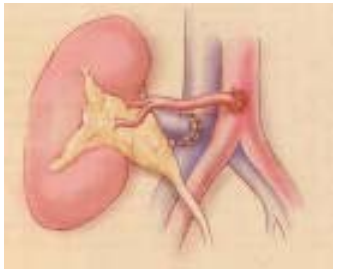
Question 2 – Which dose is necessary to reach the target?

First Steps in Man Phase I

Active principle at target?







First Steps in Man Phase I

Question 3

Did the required dose of drug reached the target?

→ **Pharmacodynamic properties**

- **Relationship between concentration at site of action and its effect**

Phase I clinical study

- **Patients:** 20 to 100 healthy volunteers
- **Length of Study:** Several months
- **Purpose:** Safety, Pharmacokinetics, Pharmacodynamics, Bioavailability, Dosage to reach the target.
- **Approximately 70% of drugs move to the next phase**

Source FDA

Optimizing Dose Regimen Phase II

Dosage? – Administration scheme?

10 mg ?

15 mg ?

Before meal?

mornings?

evenings?

once /d ?

40 mg ?

several times /d?

once /w ?

Optimizing Dose Regimen Phase II

Challenge

- Accurate information
- Limited number of patients
- Within short time

Strategic approach dependent on

- Indication
- Efficacy parameters
- Patients

Optimizing Dose Regimen Phase II

Typical number of patients

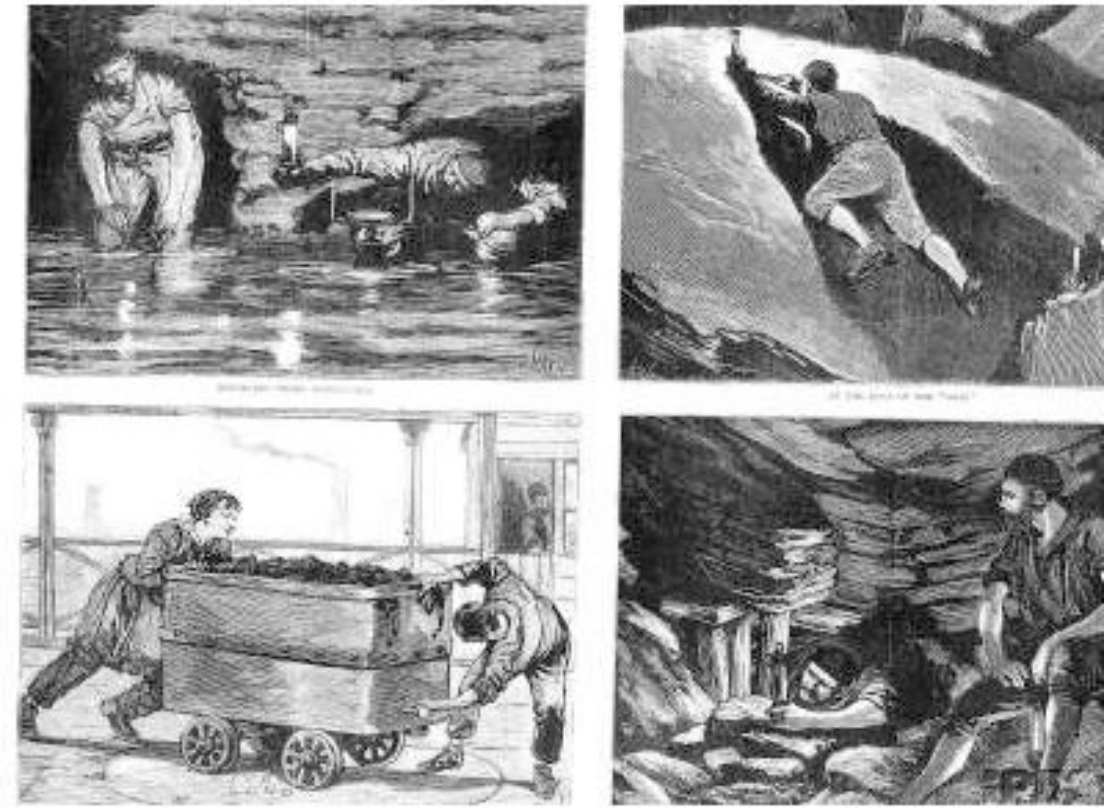
- 80 – few 100

Typical study designs

- Parallel
- Comparative (i.e. dose)
- One to few centers
- To select efficacious dose regimen

Optimizing Dose Regimen Phase II

Biomarker



Optimizing Dose Regimen Phase II

Biomarker - Definition

- a physiological response or laboratory measurement that occurs in association with a pathological process and has putative diagnostic and/or prognostic utility.
- it does not necessarily indicate efficacy or toxicity

Phase II clinical trials

- **Patients**: Up to a few hundred people with the disease/condition
- One to few centers
- Parallel/comparative
- **Length of the study**: several months to 2 years
- **Purpose**: Find efficacy dose, side effects
- Approximately 33 % of the drugs move to the next phase

Source FDA

Confirmation of efficacy and safety Phase III

Typical number of patients

- 500 – x1000

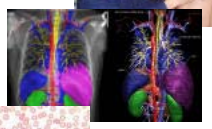
Typical study designs

- Controlled
- Placebo and/or comparative
- Double blind
- Parallel
- Multicenter and multinational
- To prove efficacy, superiority, or equivalency

Confirmation of efficacy and safety Phase III

Challenge

- Standardization of selection of patients
- Standardization of data collection
- Compliance with Good Clinical Practice



Strategic approach dependent on

- Indication
- Efficacy parameters
- Patients

Challenges in Conducting Clinical Studies

Patients

Phase III clinical trial

- **Patients** 500-3000 volunteers with the disease/condition
- Multicenter/multinational
- Length of the study: 1-4 years
- Placebo/comparative
- Double blind
- Parallel
- **Purpose**: Efficacy and monitoring of adverse effects

Source FDA

Marketing Authorization

The responsibility of authorities

http://www.emea.eu.int

U.S. Food and Drug Administration

http://www.fda.gov

http://www.swissmedic.ch

The responsibility of authorities

- Prove of quality
- Prove of efficacy
- Prove of safety