Global
Clinical
Pharmacology

From Preclinical Data to Proof of Concept – Strategies for First to Man Studies.

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Head

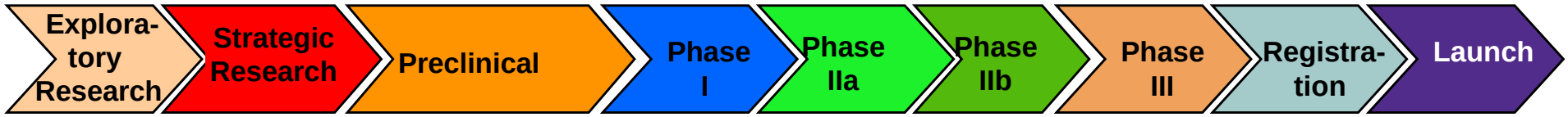
PH-GDD-GCP Pharmacodynamics

Bayer HealthCare AG, Wuppertal

Bayer HealthCare

Traditional Development Chaine

Process



Target identification

Lead structure identification

Lead structure optimization

Lead structure evaluation

FIM (Safety, Tolerability, PK)

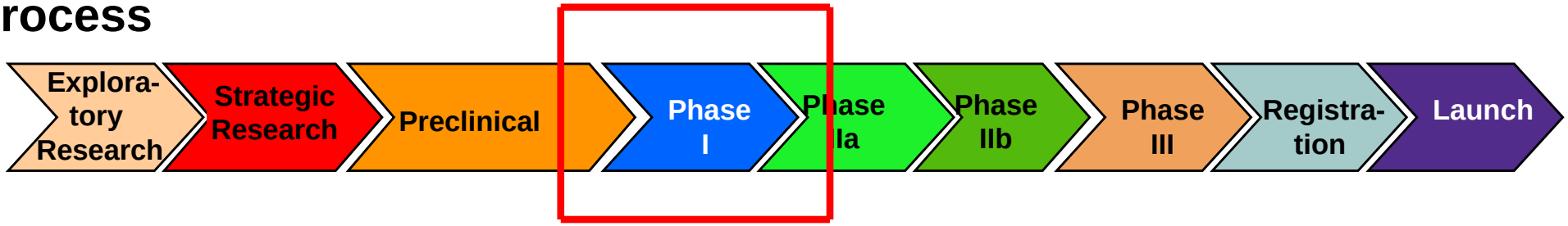
Effect, dose ranging, safety

Dose finding, safety

Efficacy, safety

Phase I Working Package

Process



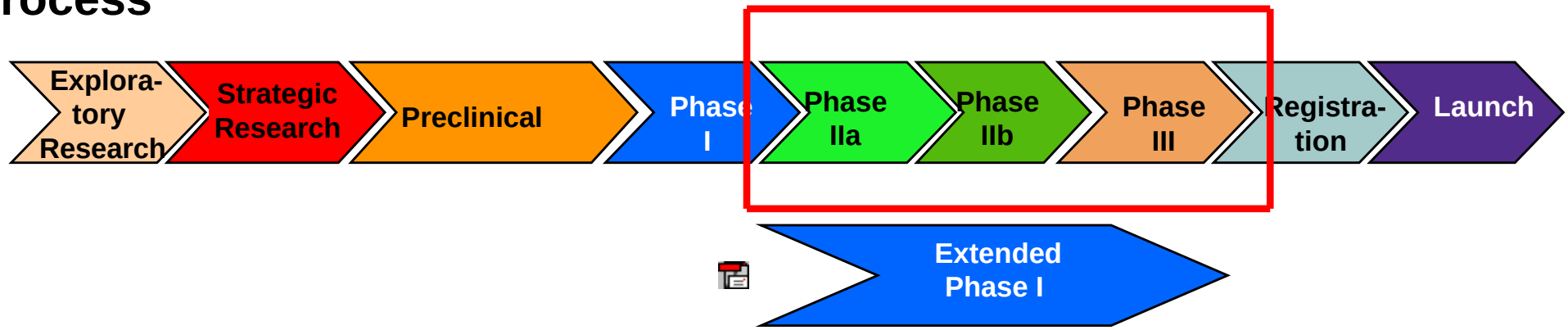
First in Man Package

- **FIM studies: safety, tolerability and pharmacokinetics (sd and md)**
- **Food effect (pilot)**
- **Effect of age and sex**
- **Critical drug interactions**
- **Comparisons of formulations if required (relative bioequivalence)**

Clinical Pharmacology is More Than “Phase I”

Clinical Pharmacology conducts about 80 % of all clinical trials until NDA

Process

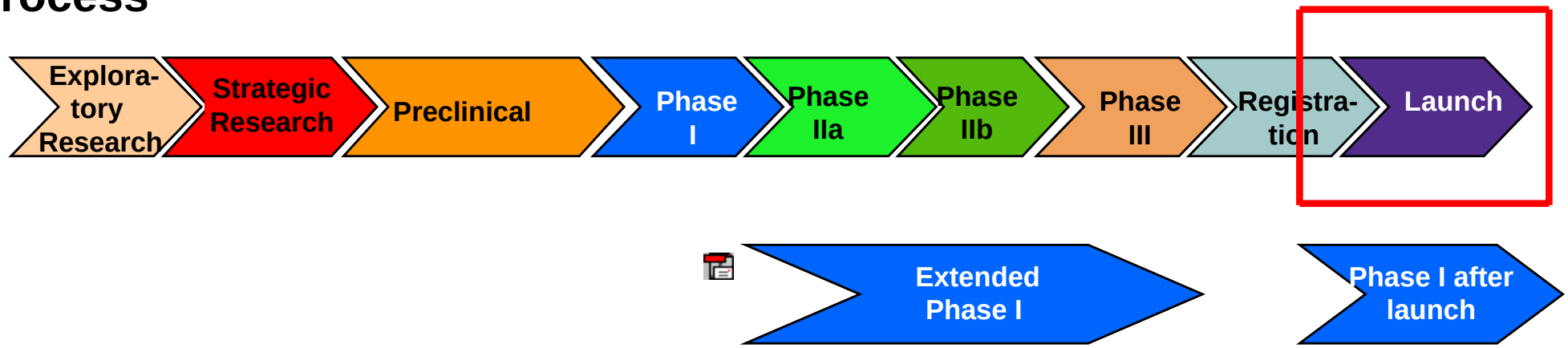


Extended phase I

- Drug interactions (pharmacokinetic, pharmacodynamic)
- Special populations (women, hepatic/renal/target pop.)
- Mass balance, Absorption site, Bioavailability
- New/alternative formulation
- Special studies

Clinical Pharmacology is Even More

Process



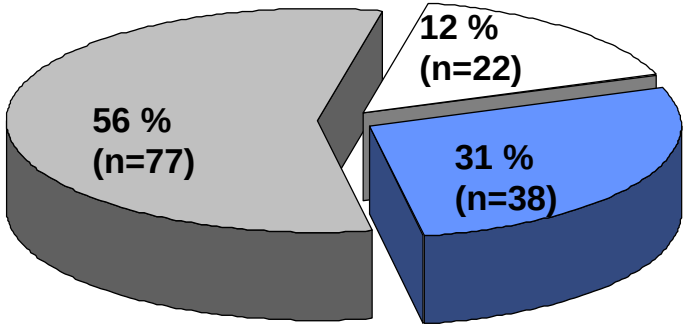
Phase I after launch

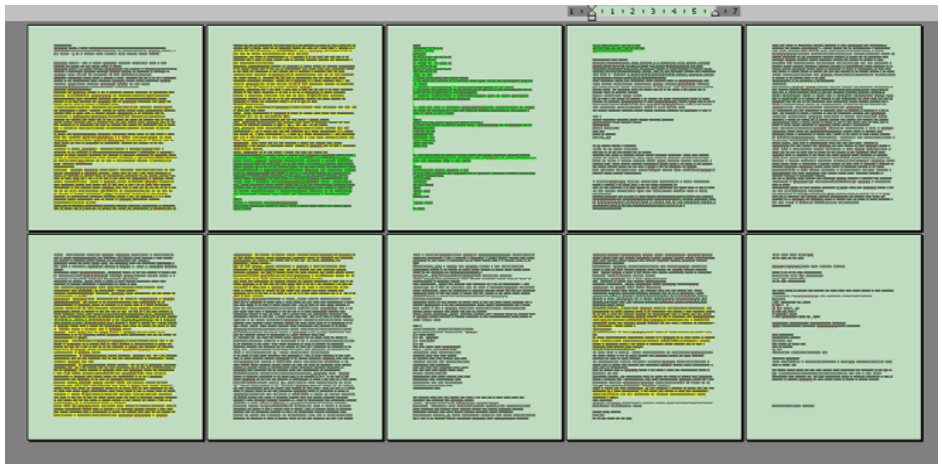
- Regulatory mandated studies
- Marketing support studies
- Studies supporting new indications
- Life cycle management

Contribution of Clinical Pharmacology to Drug Development

- **Clinical Pharmacology conducts**
  - **about 40 - 50 %of all clinical studies in a company**

Number of Clinical Trials* Year 1999





= Clinical Pharmacology

= Clinical Pharmacology / Clinical

- **Clinical Pharmacology contributes**
  - **about 40 - 50 % of information to the package insert**

Economical Pressure in Drug Development

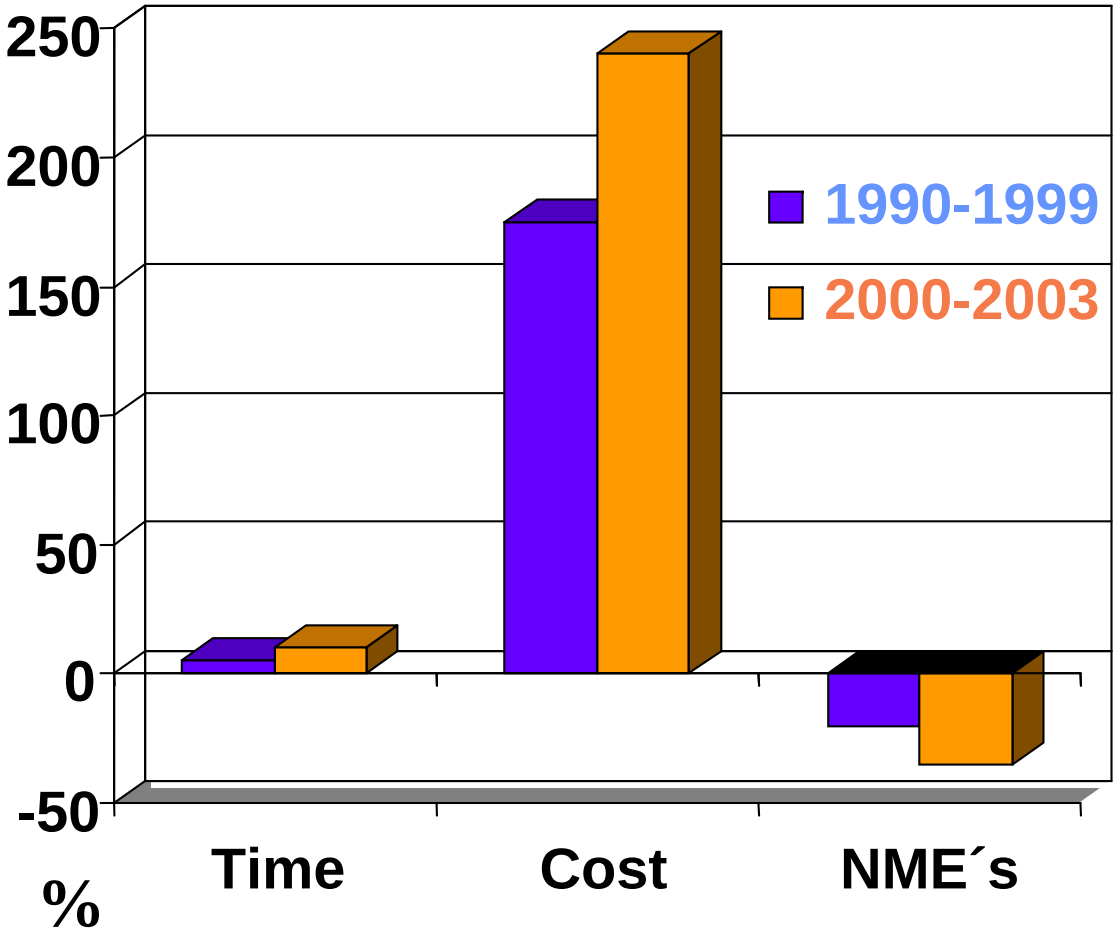
economical situation in drug industry requires from everybody working in drug development

„to do more, faster with less“

to bring new compounds earlier and more efficiently to the market

Problems in Drug Development

- increase in NCE´s released for development
- increase in development times
- increase in development costs
- failure in late clinical trials
- decrease in NME output
- reduced effective patent life
- increasing pricing regulations



- poor response rates/nonresponders after market authorization
- adverse events/withdrawal after market authorization

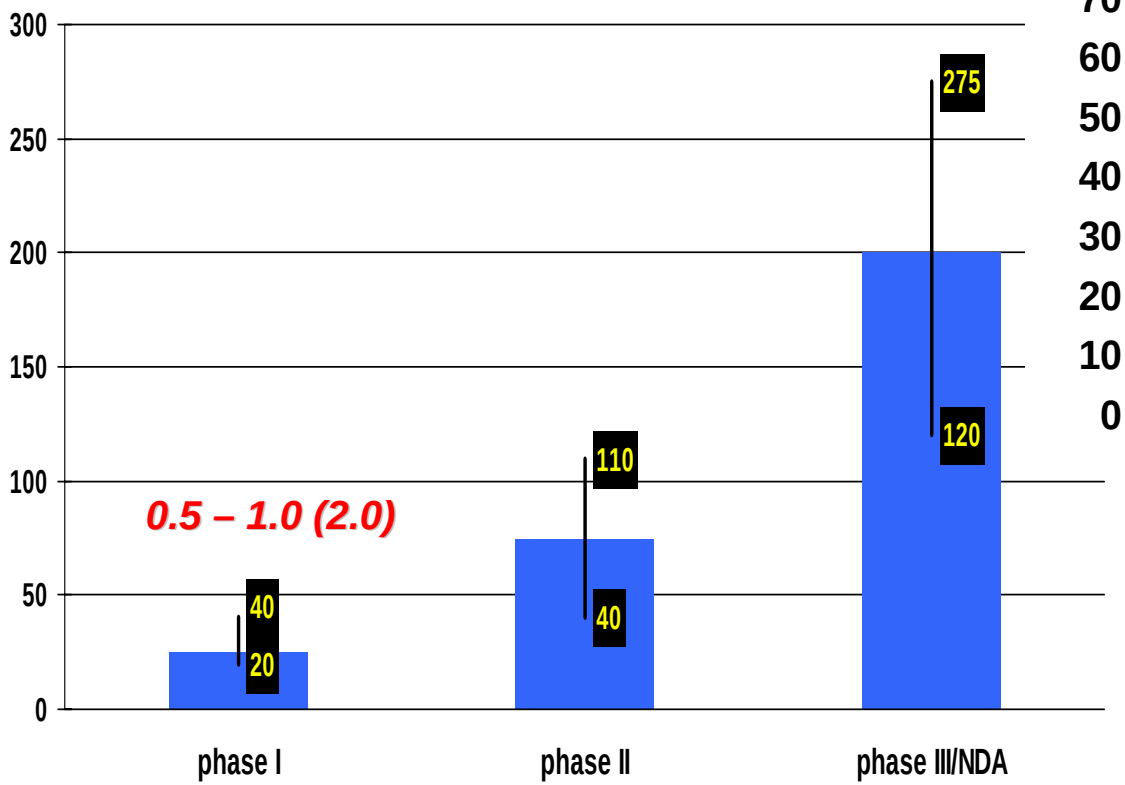
  → 2001- 2003: 15

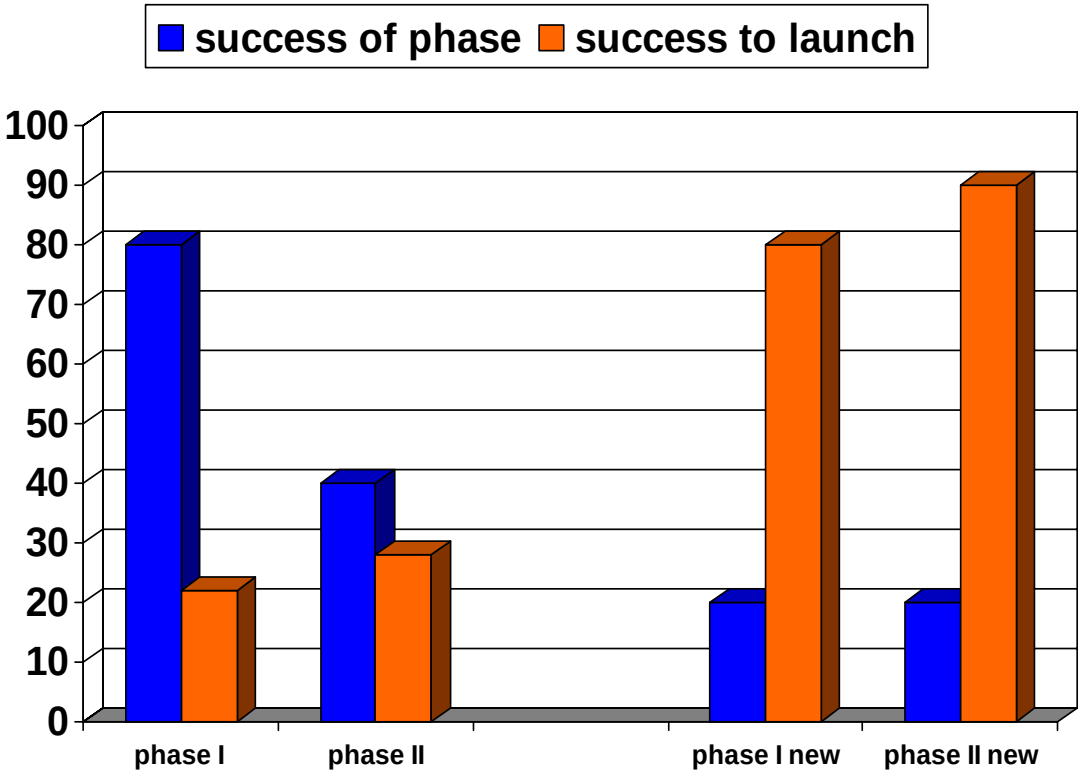
Challenge in Drug Development

- to avoid
  - to develop drugs unlikely to be therapeutically effective
  - to market new products with potential safety issues
  - to market new products lacking superiority or a better safety margin over existing treatments
- to evaluate alternative ways
  - to define the potential for a drugs safety and efficacy *earlier*

Cost and Probability of Success of NMEs in Clinical Development

Cost of drug development in clinical phases





Probability of success of NMEs in early clinical development

Economical pressure in drug development - how to deal with ?

Phase I and II studies should be designed for decision making .....

Colburn, 1996

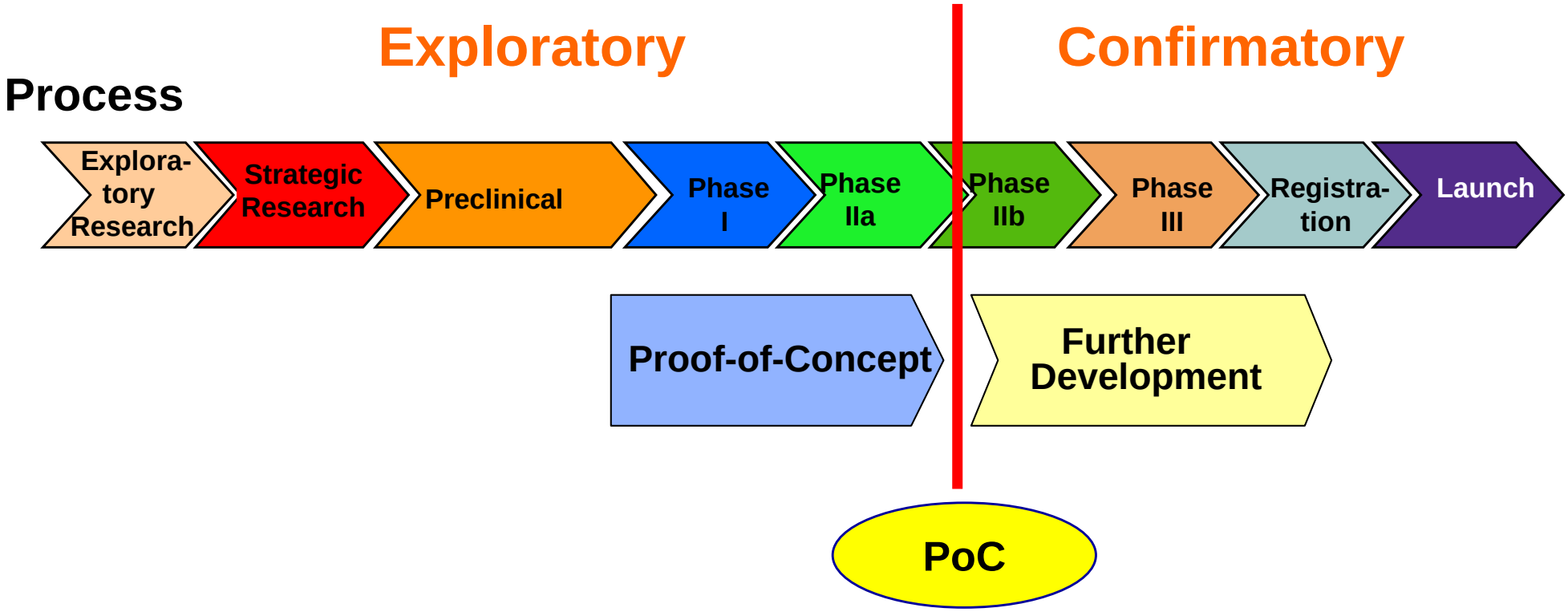
„Too often the thrust of change has been on process rather than scientific content“

Lesko et al, 2000

Reason for Failure during Clinical Develpoment

- 10 % fail because of unwanted PK/unfeasible galenics
- 20 % fail because of toxicology
- 40 % fail because of lack of efficacy
- Others (economical)

New Development Chaine



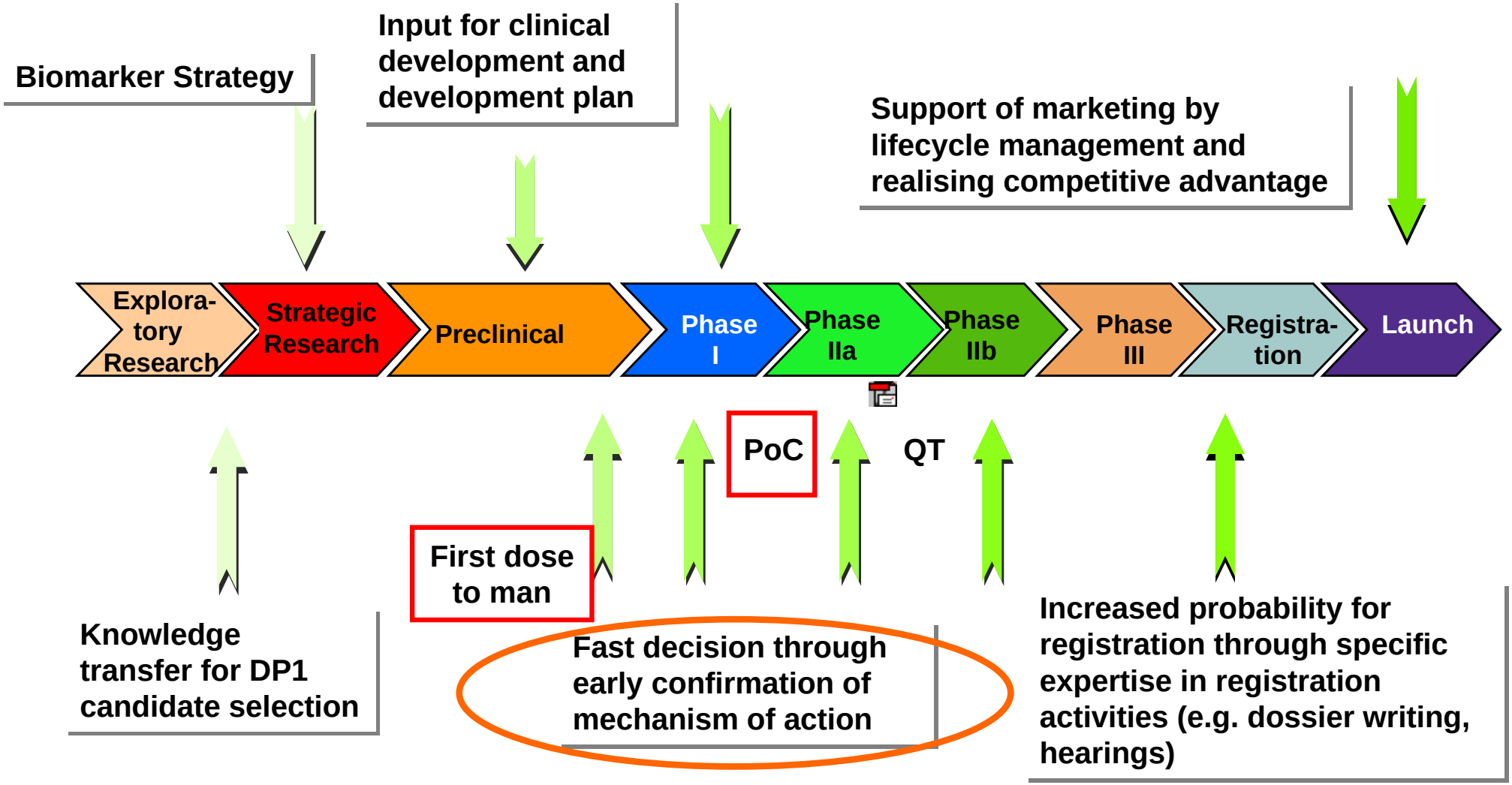
Exploratory Drug Development

- goal
  - fast entry into human
  - rapid go/no-go decision
  - minimizing resource needs in early development phases
  - reducing attrition rates in late development

- pre-requisite
  - no change in safety requirements for volunteers

- cave: does not save develoment time
  may cause additional time

Contribution of Clinical Pharmacology to Drug Development



Clinical Pharmacology is contributing to the overall development process

Exploratory and Confirmatory Phase I

Exploratory phase I

Internal decision making

- go/no-go decisions based on
  - pharmacokinetics
  - pharmacodynamics
    - safety/tolerability
    - effect (PoM/PoP)
- candidate selection
- dose, dosing regimen
  - formulation, route
- critical interactions

- individualized plan for every compound before start of preclinics
- plan studies before FIM individually

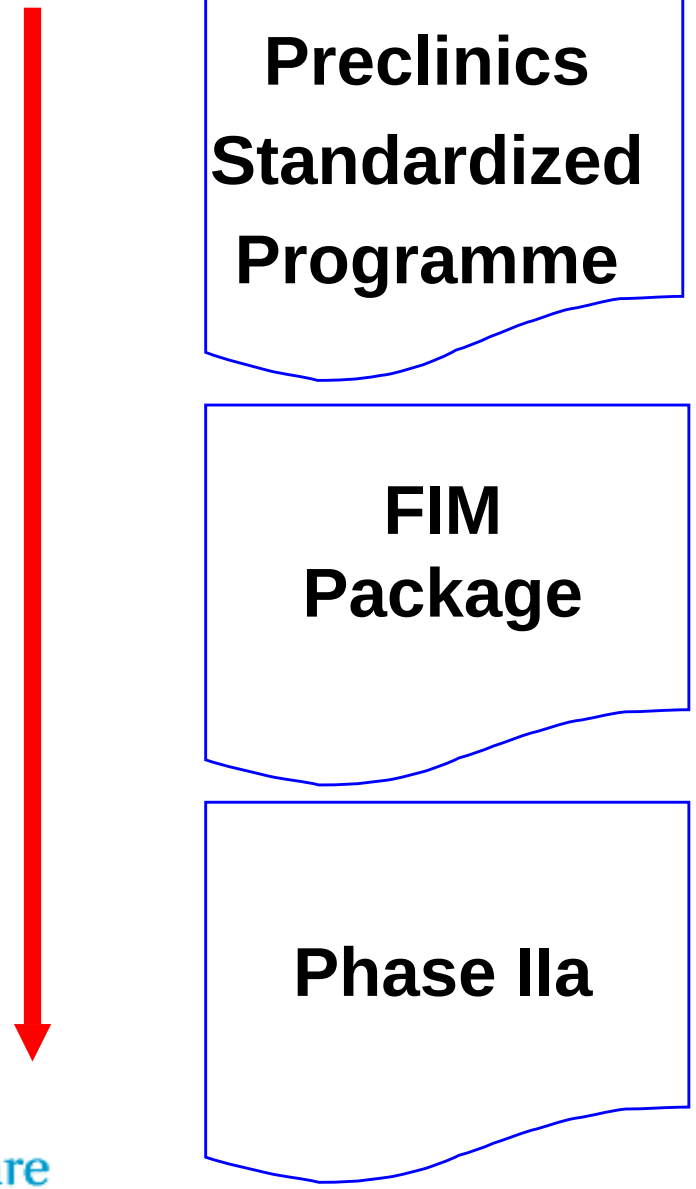
Confirmatory Phase I

Labelling

- drug interactions
  - PK and PD
- special target populations
  - Women, hepatic/renal insuf.
  - Target population
- mass balance, bioavailability
- new/alternative formulations special studies

- Concept for development before FIM

Before Exploratory Drug development



Exploratory Drug development

Preclinics Focused Programme	Preclinics Focused Programme	Preclinics Focused Programme
Phase I go/no-go SD/MD/INT	Phase I SD	Phase I (vol. or pat.) SD & MD
	PoM/PoP	PoM/PoP „Phase I“ Setting
		PoM/PoP „Phase IIa“ Setting

Exploratory Phase I

- **Mandatory:**
  - **First into man (SD): safety, tolerability, PK**
    - **but may only comprise limited number doses**
  - **Proof of Mechanism/Proof of Concept study**
    - **May be incorporated in FIM Study (PoM via lab. Biomarkers)**
- **Optional:**
  - **First into man (MD): safety, tolerability, PK**
  - **Food effect (pilot)**
  - **Effect of age and sex**
  - **Critical drug interactions**
  - **Comparisons of formulations if required**
  - **Absorption Site**
- **Integration of biomarkers whenever possible**

Exploratory Drug Development

- goal
  - fast entry into human
  - rapid go/no-go decision
  - minimizing resource needs in early development phases
  - reducing attrition rates in late development

- pre-requisite
  - no change in safety requirements for volunteers

- cave: does not save develoment time
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Biomarker/surrogate/clinical endpoint - Definitions

- **Biomarker:** laboratory measurement or physiologic sign in association with physiologic process of putative therapeutic or diagnostic value
- **Surrogate endpoint:** laboratory measurement or physiological sign used as substitute for a meaningful clinical endpoint
- **Clinical endpoint:** clinical meaningful measure of how a patient feels, functions, survives
- **used for safety and efficacy**

Lesko et al CPT, 2001

What is a Biomarker?

- **Type 0:** genotype/phenotype
- **Type 1:** plasma concentration
- **Type 2:** target occupancy
- **Type 3:** target activation
- **Type 4:** physiological measures
- **Type 5:** disease process
- **Type 6:** clinical scales

Dahnhof et al, Pharmaceutical Research 2005

First in Man Study

- **Study design:** Randomised
  non-controlled or placebo-controlled
  single- or double-blind
  cross-over or group-comparision
  usually monocentre studies
- **Objectives:** Safety , tolerability, pharmacokinetics, pharmacodynamics
- **Subjects:** Healthy (male) subjects, symptomatic subjects (mildly-diseased)
- **Variables**
  - **Safety: Lab, vital signs, clinical measures (depending on compound and indication, subjective symptoms, questionnaire)**
    - **Nature of adverse events, maximum safe dose, reversibility countermeasures**

First in Man Study

- **Pharmacokinetics (drug and (active or major) metabolites): bioavailability, Cmax, tmax, t1/2, clearance, AUC, Vss**
  - **dose linearity/proportionality**
  - **bioavailability (absolute/relative)**
  - **interactions**
  - **age/gender**
  - **special populations**
- **Pharmacodynamics: variables depending on compound and indication, usually non-invasive**
  - **pharmacological profile**
  - **onset, duration, extent and variability of effects**
  - **interactions**
  - **age/gender**
  - **special populations**
- **PK/PD relationship**
  - **Dose/concentration effect relationship**
  - **Modelling and Simulation**

- **Formulation: service formulation possible**

Adverse Events in Healthy Volunteers in Phase I Studies - Overall Results

Adverse events in 1559 volunteers with 2955 treatments

	active drug	placebo	total
follow-up (days)	25802	3862	29664
adverse events (n)	2192	153	2604
incidence (%)	9.1	8.5	8.8
incidence (%) placebo-contr.	14.1*	9.1	12.1

Lutfullin, Kuhlmann, Wensing IJCPT, 2005

Rates of occurence of adverse events in healthy volunteers in phase I studies

	Sibille	Bayer
number	1558	2604
per subject	1.5	1.7
per treatm.	1	0.9
per study	29	18.3
mild/moderate %	97.2	99.2

Sibille et al, Eur J Clin Pharm 1998

Lutfullin, Kuhlmann, Wensing IJCPT, 2005

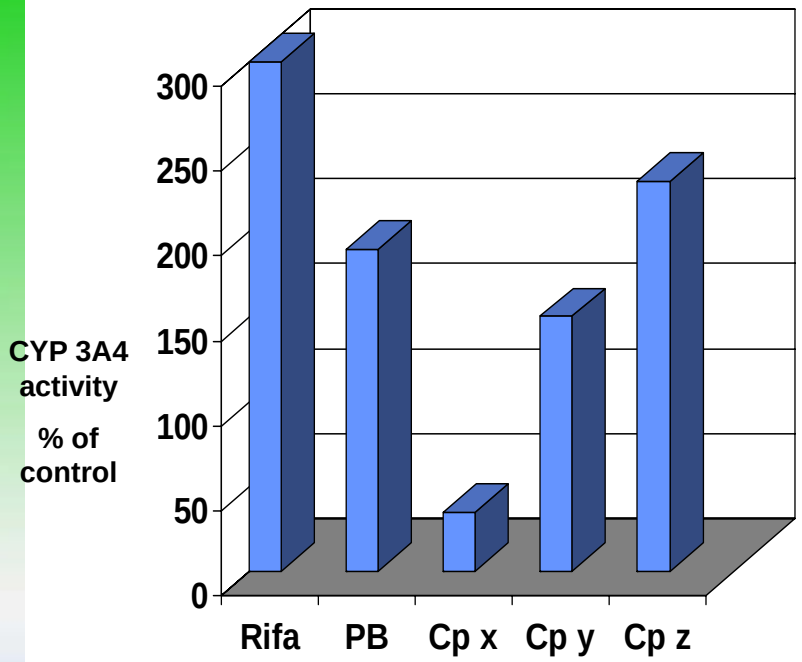
Considerations for Early PoM/PoC in Phase I/IIa

- → definition of study population
  - → healthy volunteers
  - → patients with mild disease (symptomatic volunteers)
    - ⇧ no disadvantage if no efficacy
    - ⇧ no concomitant medication
- → validated biomarker
  - → feasibility in preclinical models
  - → established PK/PD relationship
  - → exploratory markers may be useful
- → safety first
- → availability of adequate formulation
  - ➢ usually service formulation (solution)/iv formulation
    - ⇧ keep bioavailability problems low
    - ⇧ feasibility in patients
- → focused preclinical program to support phase I up to PoP/PoM
- → focused phase I program to support PoP/PoM study
    - ⇧ single/multiple dose escalation
    - ⇧ special populations

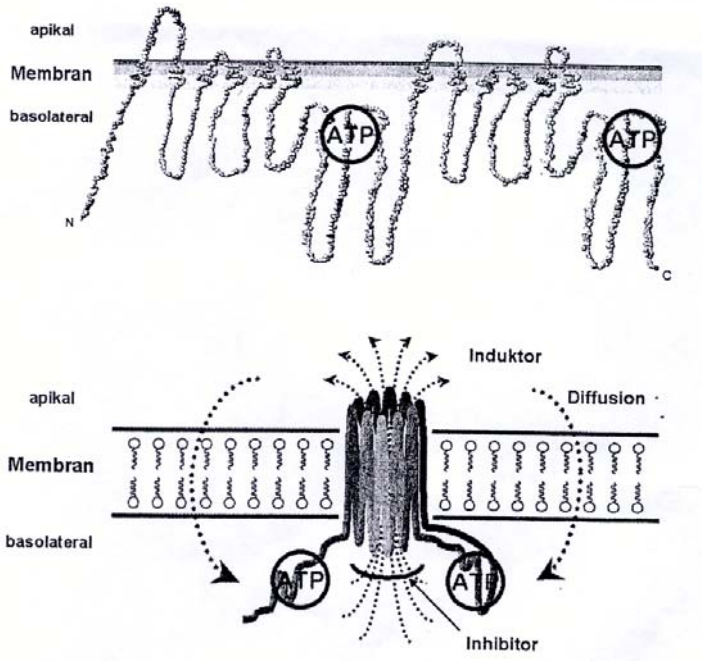
Phase Ib/IIa: Proof of Concept

- **Design:** randomised
  placebo/competitor controlled,
  exploratory,
  double-blind
  single or multicentre trial (few centres only)
- **Objective:** Measurement of pharmacological activity
- **Subjects:** Healthy subjects or mildly diseased patients
- **Variables:** Biomarkers (surrogates) depending on indication
- **Treatment:** short term (up to 4 (-6) weeks), limited number of doses and subjects (50-100)
- **Formulation:** service formulation possible

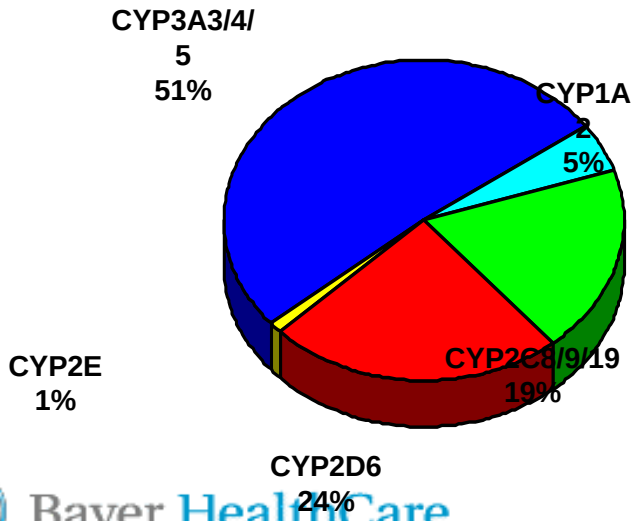
Preclinical Pharmacokinetics



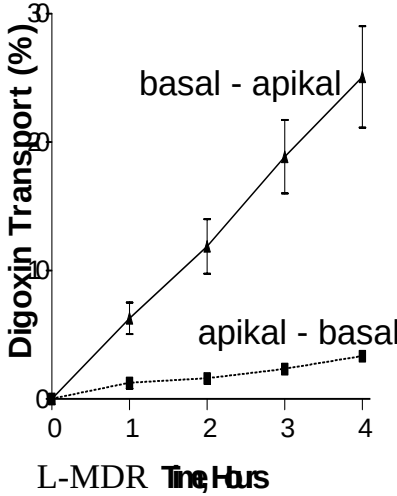
Rifa = Rifampicin
PB = Phenobarbital
Cp x = Compound x
Cp y = Compound y
Cp z = Compound z

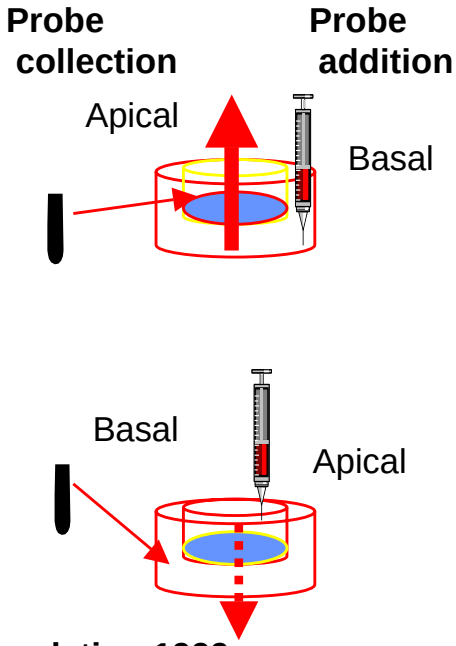


CYP 3 A4 enzyme induction in human hepatocytes



[^{3}H]-Digoxin Transport





Fromm et al, Circulation 1999

Preclinical Pharmacokinetic Information

Information from basic pharmacokinetics in different species

- interspecies comparison
- absorption/elimination
- responsible enzymes
- most human like species
- polymorphic enzymes (2D6, 2C19)
- enzyme induction
- enzyme inhibition
- *drug-drug interactions*
- *involvement of transporters*
- *absorption site*

Information for phase I design

- go/no-go, up-scaling, interaction program, risk assessment

Exposure Predictions for Exploratory Phase I

- **Estimation of likely human exposure (AUC and Cmax) for first dose in man**
- **Estimation of doses likely to be safe based on exposure in preclinical safety/toxicology studies**
- **Estimation of doses likely to be effective based on exposure in pharmacological studies**

Determination of First to Man Dose

Safety Margin Considerations

Desired Effects

mouse in-vitro EC_{50} 500 nM human in-vitro EC_{50} 48nM

rat in-vitro IC_{50} 450 nM

mouse in-vivo C_{max} 3.1 µM (~1.5 mg/l @ 1.25 mg/kg bid) human (pred.) C_{max} ~0.5 µM (0.2 mg/l @ 0.35 mg/kg)

f_u 0.086 % ⇒ $C_{max,u}$ ~0.43 nM

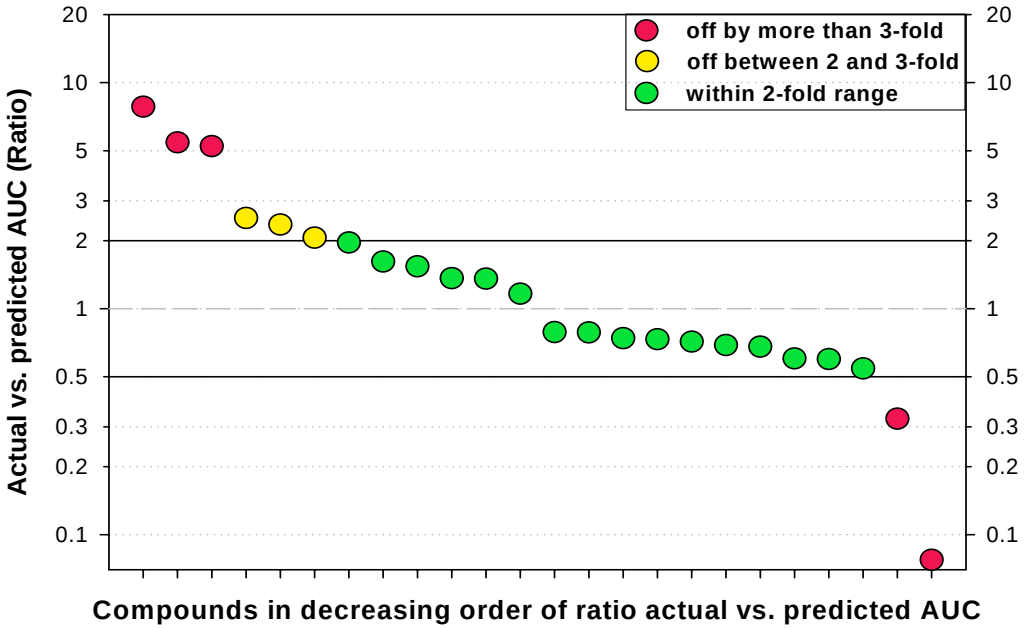
Adverse Effects

		Safety Margin
HERG in-vitro	EC_{50} ~3 µM (EC_{20} ~1 µM)	2
Purkinje fiber APD_{90} shortening at	≥ 1 µM	2
consc. dog: no effects on ECG / heart rate		
	C_{max} ≤ 8.0 mg/l (≤ 16.7 µM)	> 33
	f_u 0.138 % ⇒ $C_{max,u}$ ≤ 23 nM	> 53

Proposed human starting dose: 0.1 mg/kg or 10

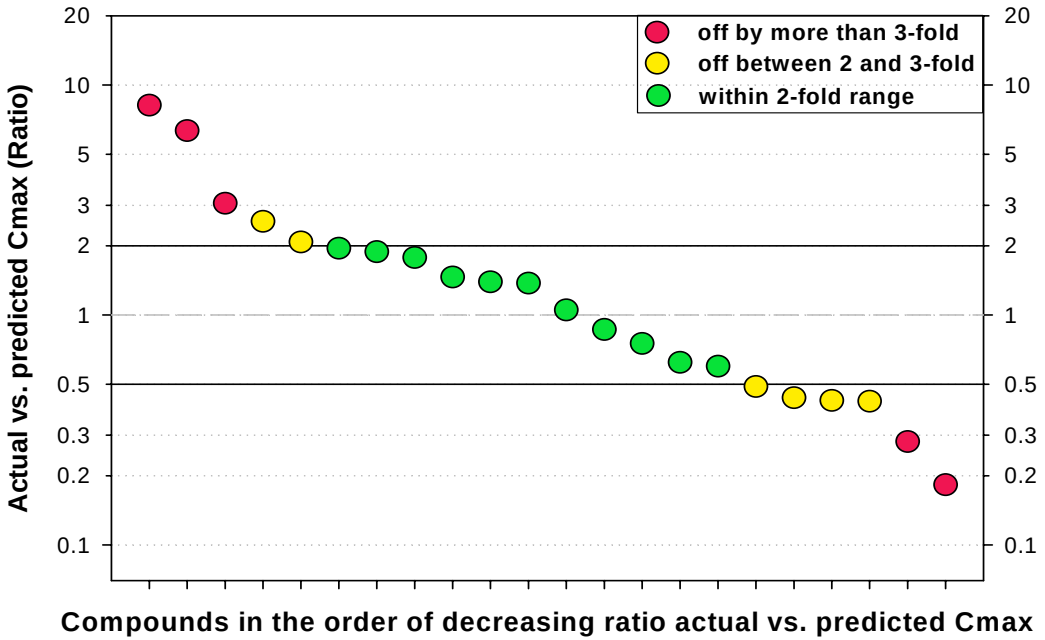
Determination of First to Man Dose - Species Scaling

AUC n=24



67 % within a factor of 2
79 % within a factor of 3

C_{max} n=24



55 % within a factor of 2
77 % within a factor of 3

Preclinical Pharmacodynamics

Experimental Pharmacology

Toxicology

Safety Pharmacology

formally well standardized (ICH-Guidelines; standard models)

but

often uncertainty about physiological relevance of target in man

Safety Pharmacology

- **investigation of the effect on important physiological systems**

  → **mandatory (ICH)**

  ⇧ **cardiovascular, respiratory, central-nervous**

  → **additional (dependent on drug class, indication)**

  ⇧ **gastro-intestinal, excretory, endocrine, blood, metabolism etc.**

  ⟶ **dose-response relationship**

- **special investigations**

  → **pyrogenicity, immunotoxicity, hypersensitivity**

Duration of Toxicology Studies

Duration of toxicology studies required before starting studies in humans

Clinical treatment	Duration of toxicity studies duration		
	EU	USA	Japan
single dose	2 weeks	2 weeks*	2 weeks (non-rodent)
		4 weeks (rodent)	
multiple dose			
up to 2 weeks	2 weeks	2 weeks	2 weeks (non-rodent)
			4 months (rodent)
up to 1 month	1 month	1 month	1 month
up to 3 months	3 months	3 months	3 months
up to 6 months	6 months	6 months	6 months
> 6 months	6 months (rodents)		6-9 months (non-rodents)

* alternative: single dose with extended examinations

Preclinical Pharmacodynamics

- **predictions for use in man**
  - **„therapeutic effect“ in relevant animal model**
    - **target concentration, minimum/ maximum effective dose**
    - **dose-effect relationship**
    - **type of pharmacological measures to be used in man**
  - **toxicological/safety pharmacological targets**
    - **NOAEL**
    - **safety margin**
    - **type of precautions to taken in phase I**
    - **availability of decision making data (QTc)**
  - **effect of sex, age, disease**

- **need of biomarkers validated in preclinical studies**
  - **availability and use feasible in man**

Preclinical Evaluation

- compound characteristics
  - → high lipophilicity, low solubility
- meaning of target
- meaning of pharmacological model
- adequate description of dose/concentration-effect relationship
  - → same species for all preclinical disciplines
  - → relevant doses and time course, adequate number of animals
  - → consistency of formulations in human and preclinical studies
- availability and use of biomarkers also feasible in humans
- availability and interpretation of required toxicological and safety pharmacological data
  - toxicokinetics
- description of metabolic pathways
  - → most human like species, responsible and polymorphic enzymes, enzyme induction and inhibition QTc (HERG Channels), polymorphisms

Screening IND - I

- **question: are single dose toxicology studies adequate to support s.d. phase I studies ?**

  Monroe & Mehta (1996) Clin Pharmacol Ther 59: 258-264

- **FDA response (1996) Clin Pharmacol Ther 59: 265-267**

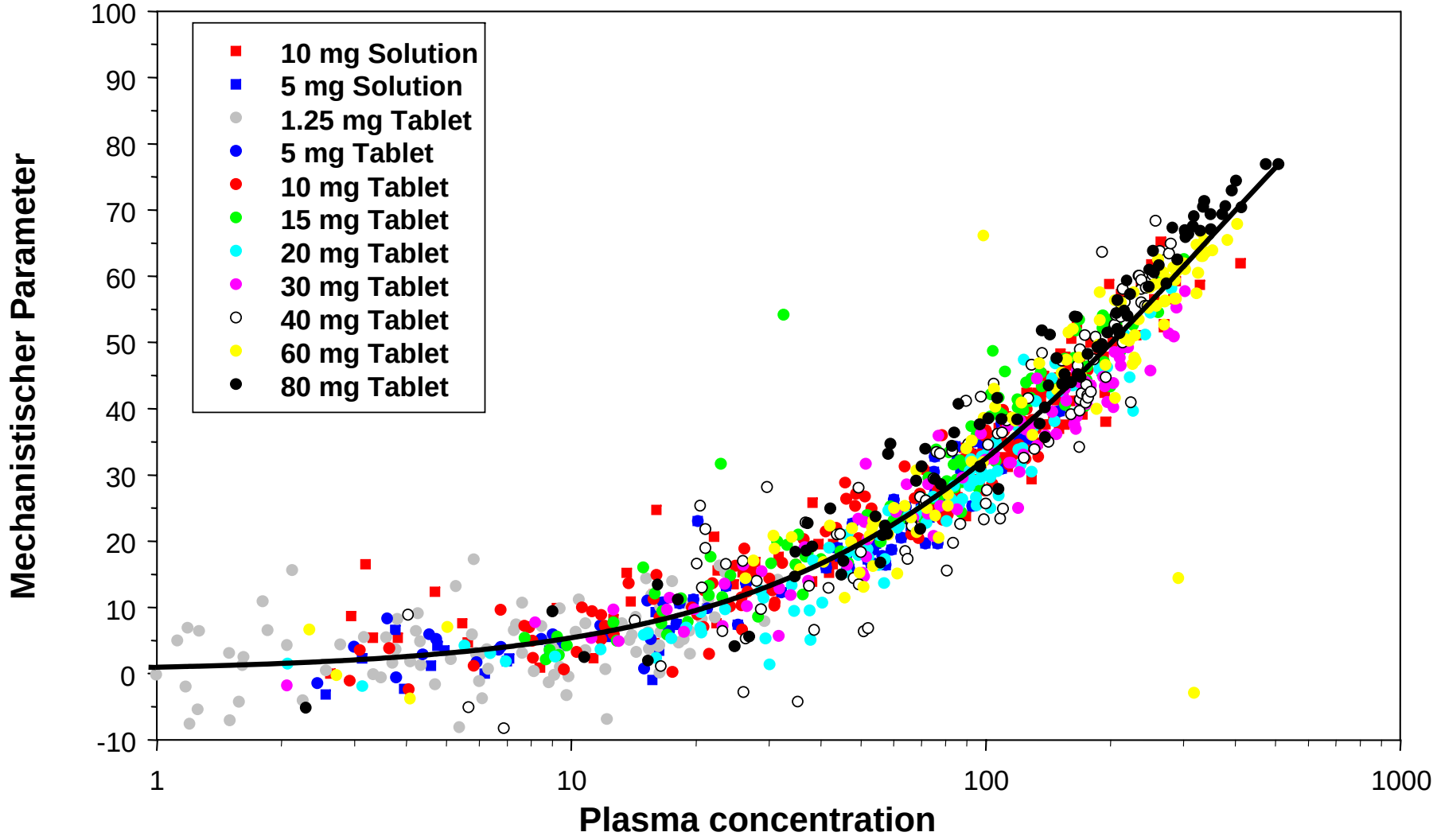
  guidance for s.d. animal tox to support s.d. phase I studies
  - **2 mammalian species**
  - **2 routes of administration**
  - **wide range of doses incl. doses to cause life-threatening toxicity**
  - **male and female gender**
  - **observation for 14 days after dosing**
  - **histopathologic evaluation of all major organs and tissues (early and late - reversibility?)**
  - **toxicokinetics with validated assays**
  - **complete preclinical pharmacology efficacy program**

Own single dose approach

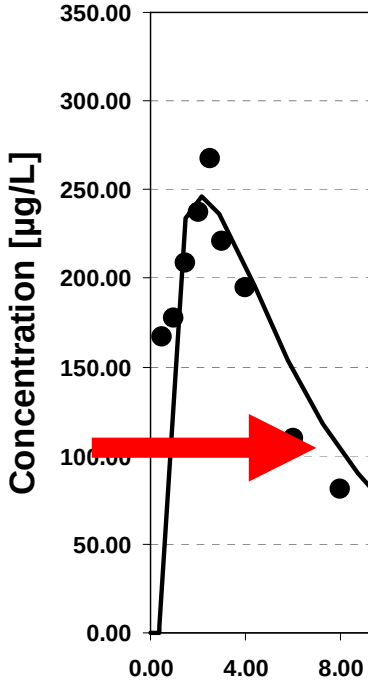
- toxicology
  - s.d. tox. study rodent (clinical route)
  - 14-day study in rats (formulation maximising exposure)
  - 14-day study in non-rodent (formulation maximiszing exposure)
  - genotoxicity tests covering two different endpoints
    - e.g. Ames and micronucleus
    - reversibility should be built in the 14-day studies
- inclusion of 14-day studies offers more flexibility
  - e.g. start of up to two week studies in man
- safety pharmacology
  - traditional program
    - some parameters substituted by toxicology
    - if only s.d. toxicology available: full program needed

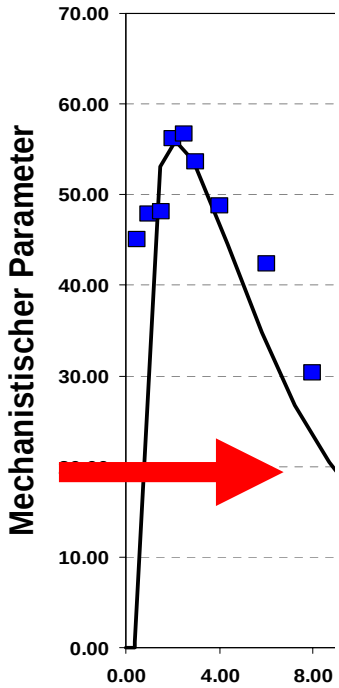
SD FIM and PoM - Laboratory Biomarker

Concentration-Effect Relationship for a Direct Factor Xa Inhibitor

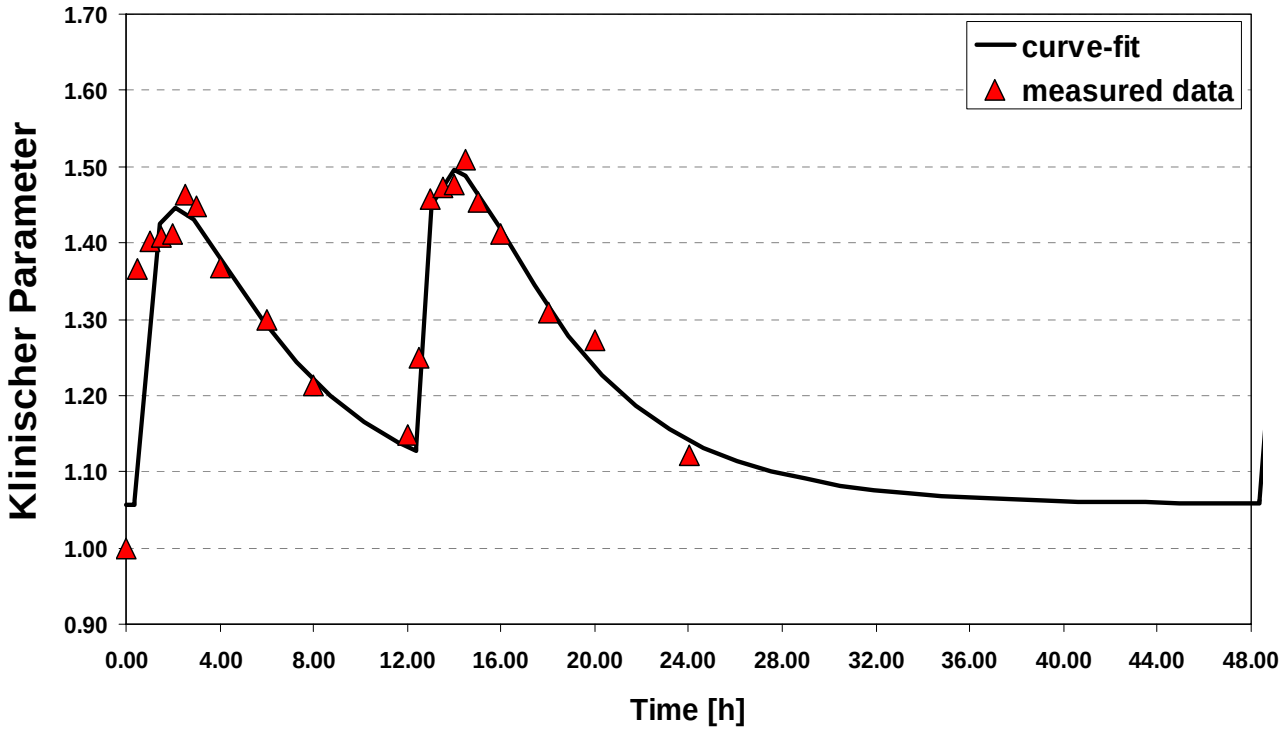


Prediction of Plasma Concentrations and Pharmacodynamic Effects





observe and model



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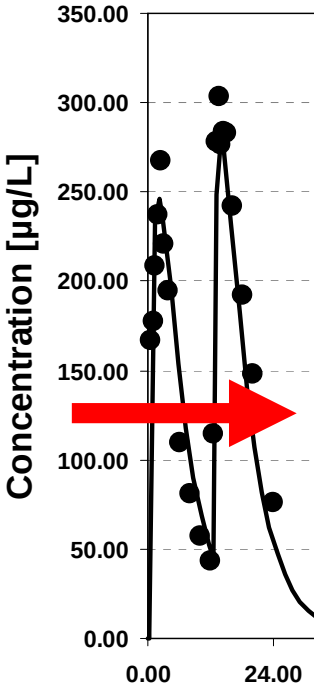
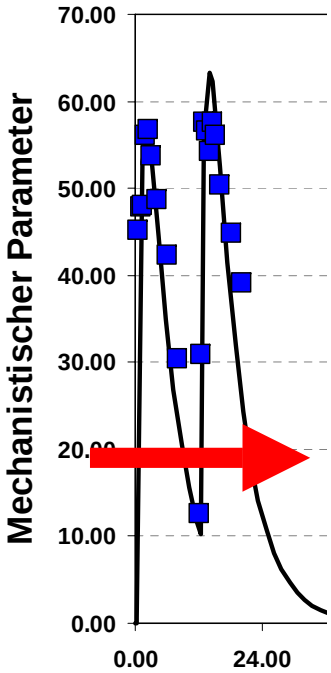
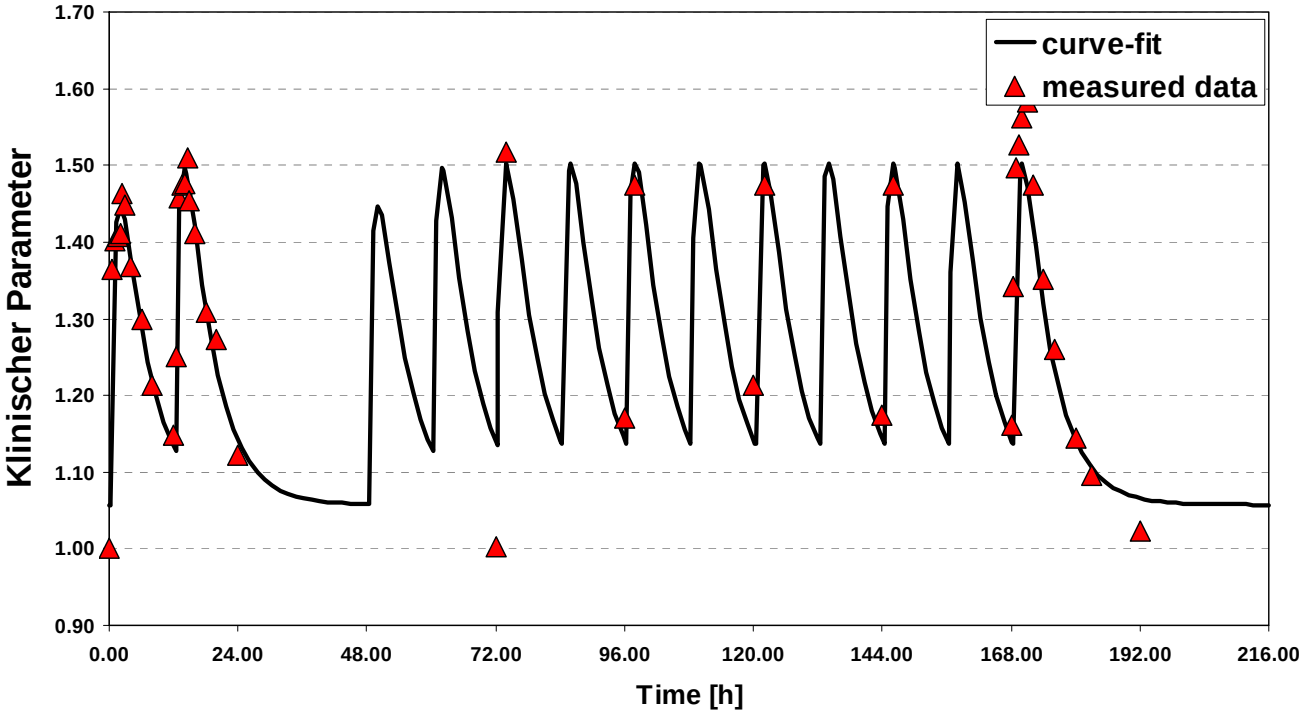
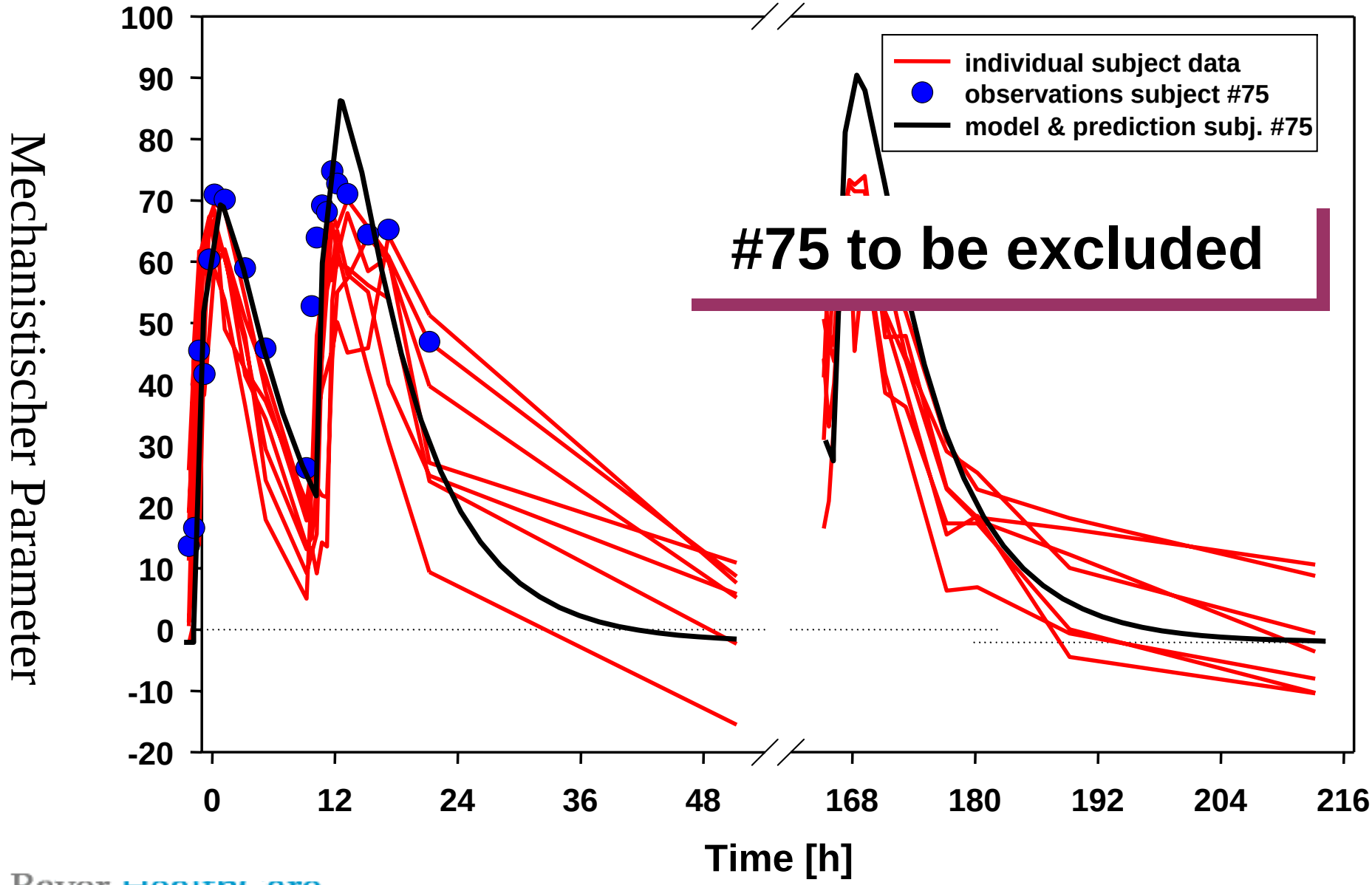




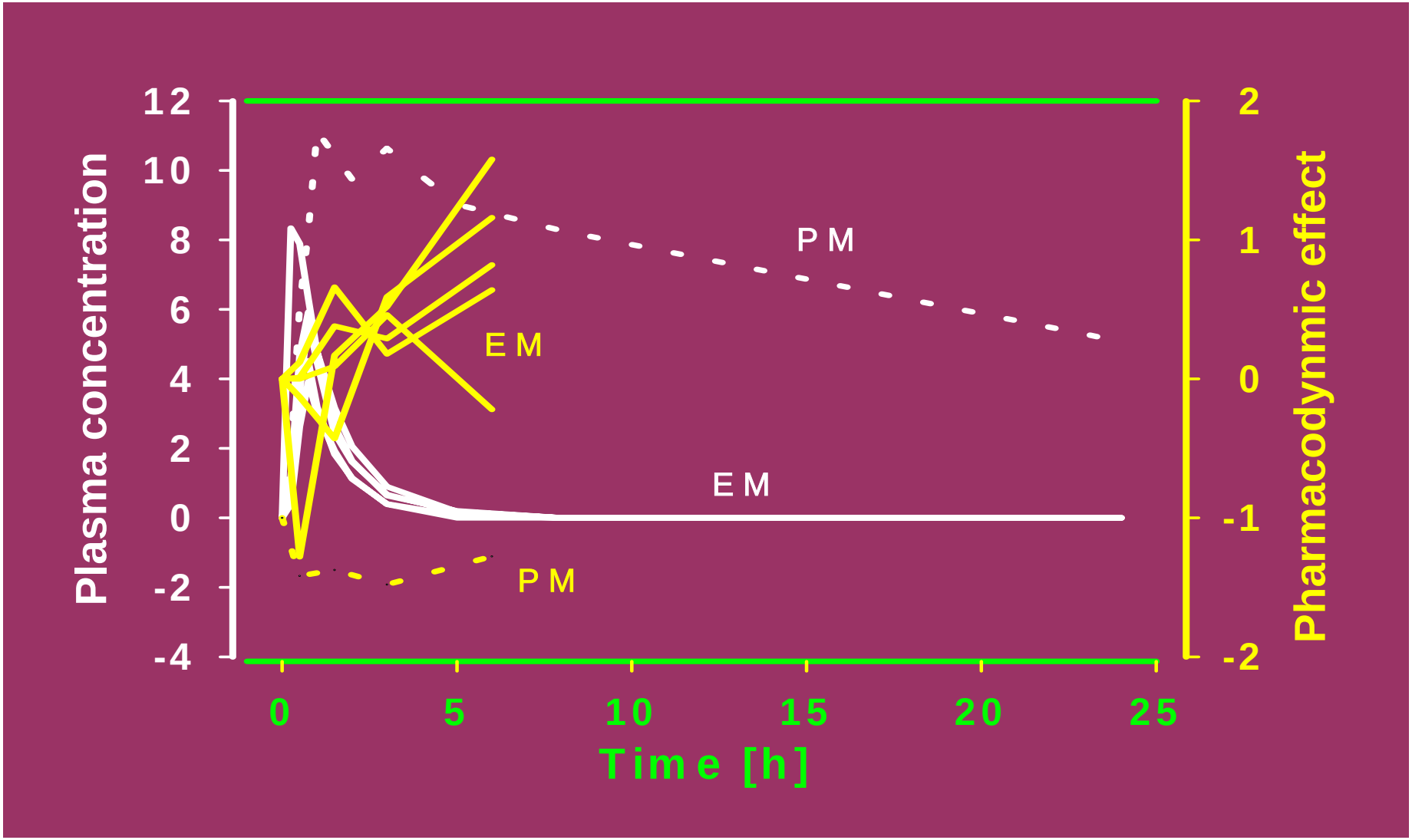
predict and verify



Prediction of Plasma Concentrations and Pharmacodynamic Effects

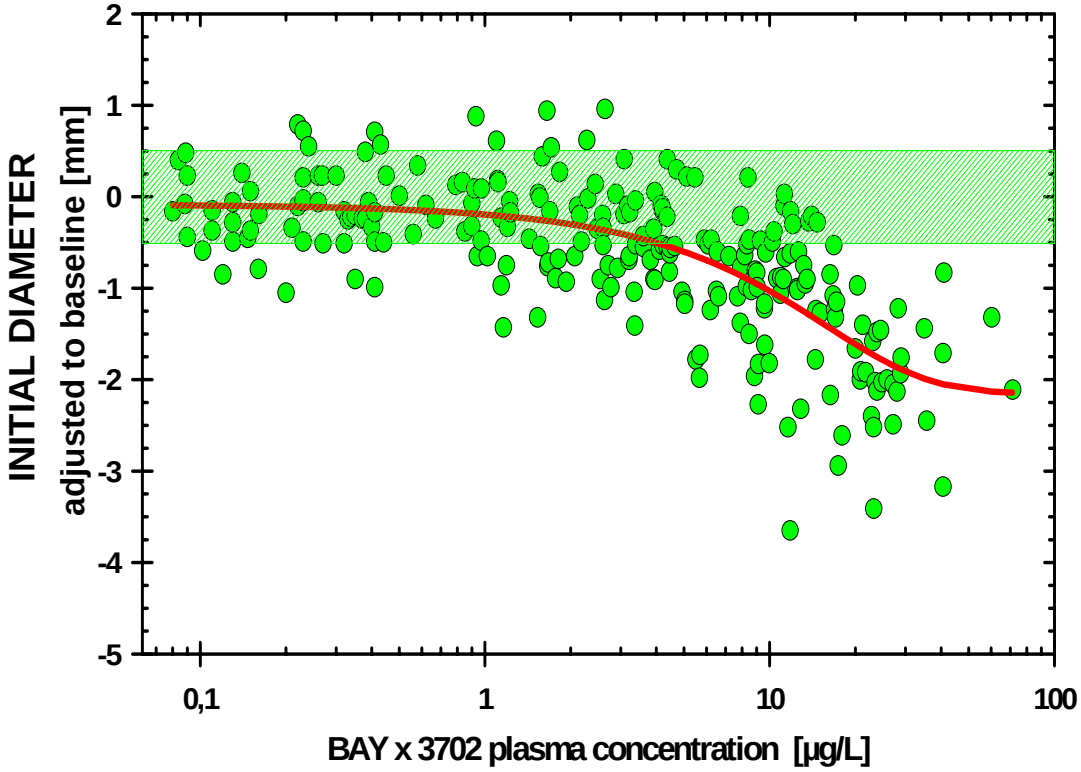


Sd FIM - PK and Exploratory Biomarker

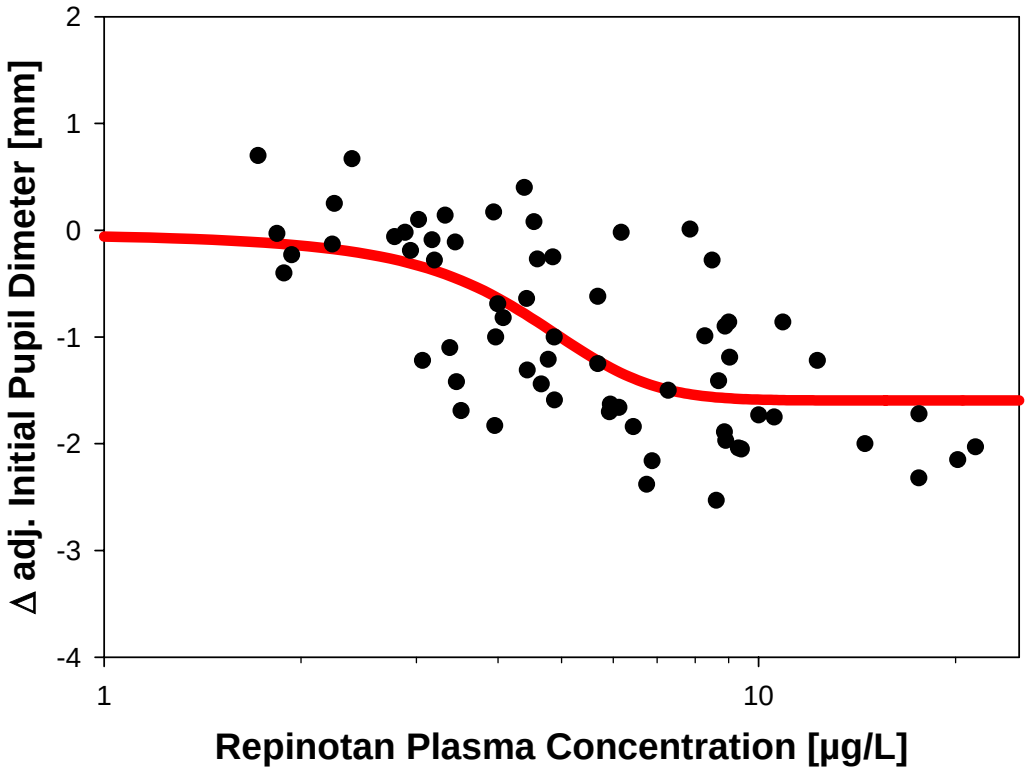


Pupillopgraphy as Exploratory Biomarker Concentration-Effect Relationship

Healthy Volunteers

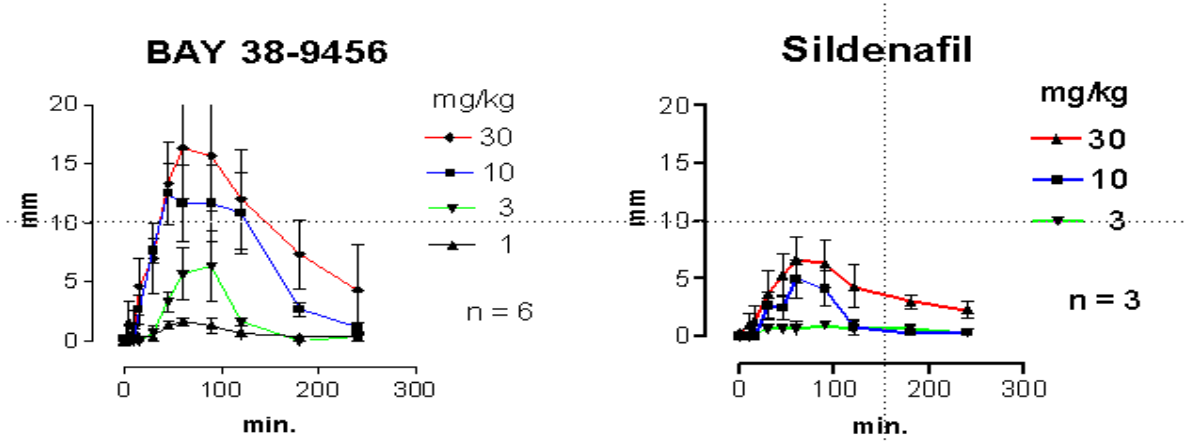


Patients



Sd phase I data (200-2000 µg, p.o.)

SD PoP - Clinical Biomarker in Healthy Volunteers

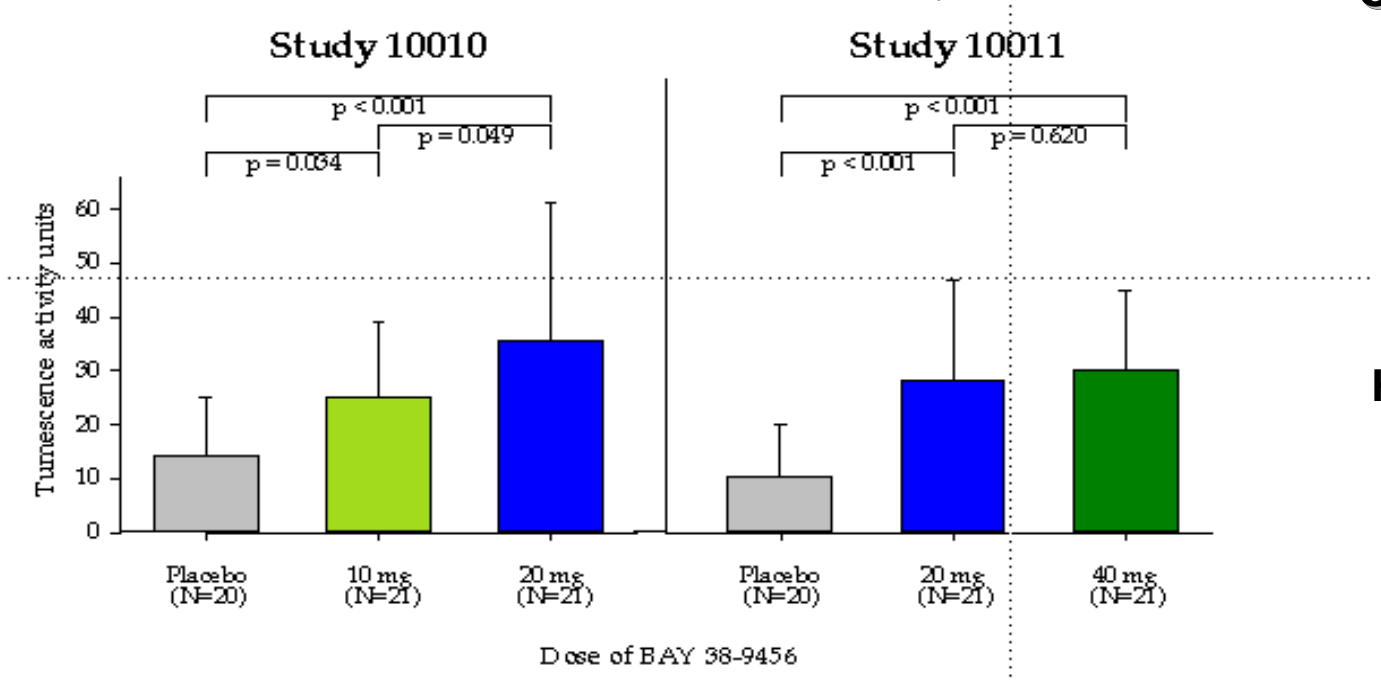


Animal experiment

⇨ BAY 38-9456 induces much stronger erections than Sildenafil

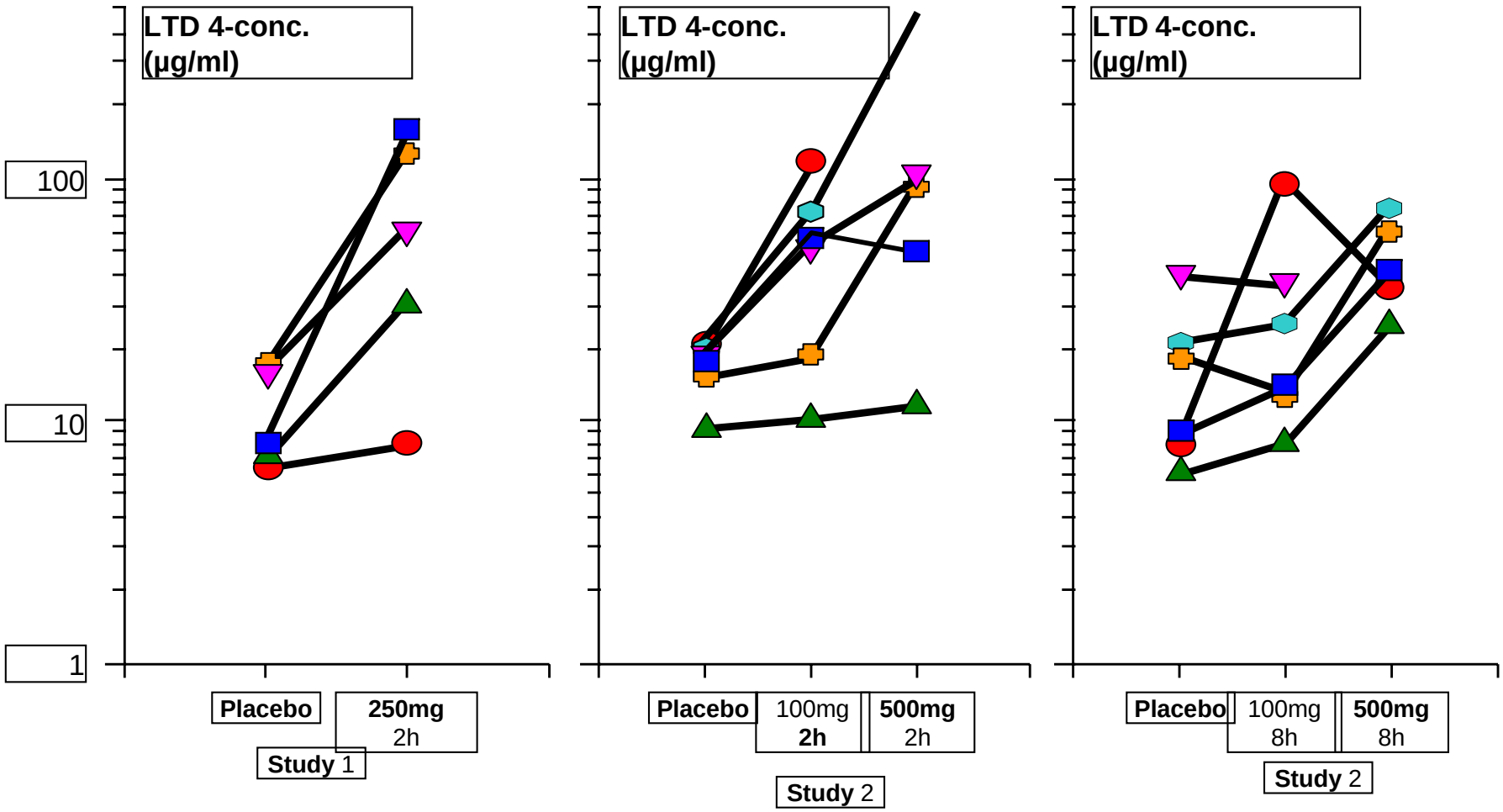
⇨ The maximal Sildenafil effect can be achieved with 10 x lower doses

Levitra effects after oral administration



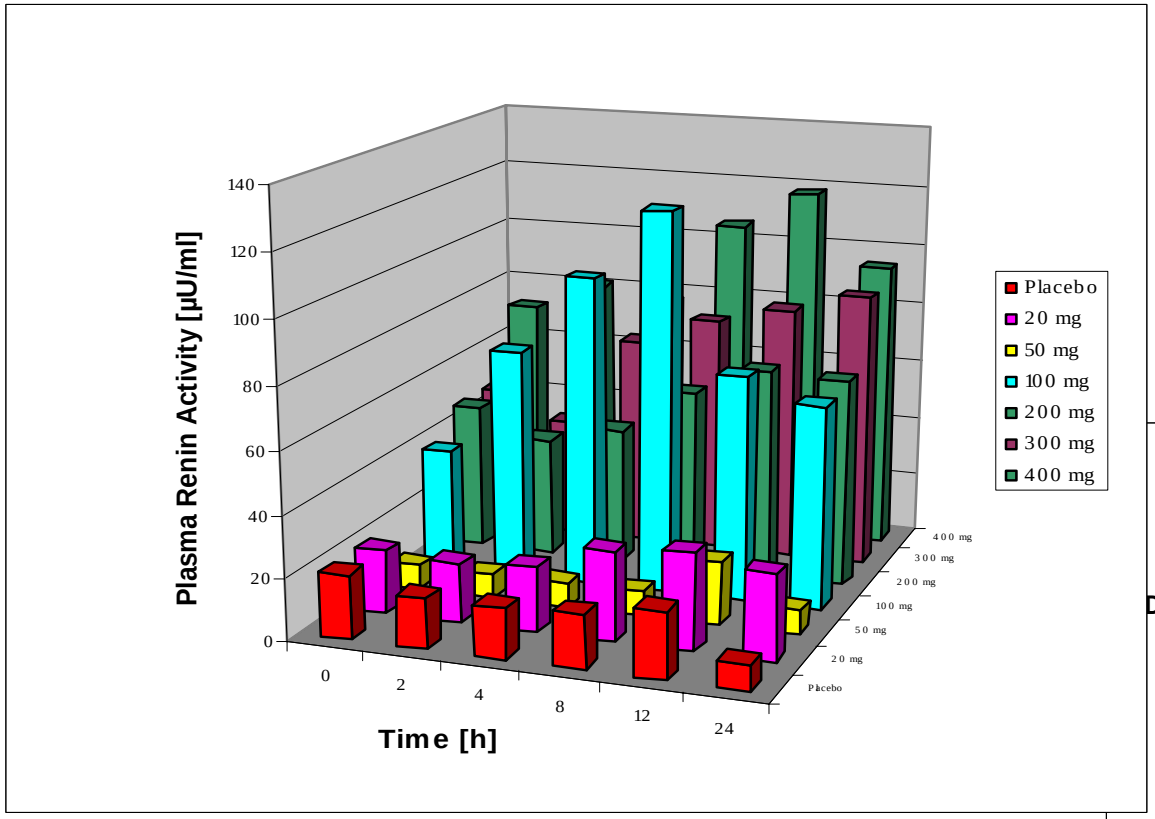
Healthy volunteers

SD PoP - Clinical Biomarker in Healthy Volunteers

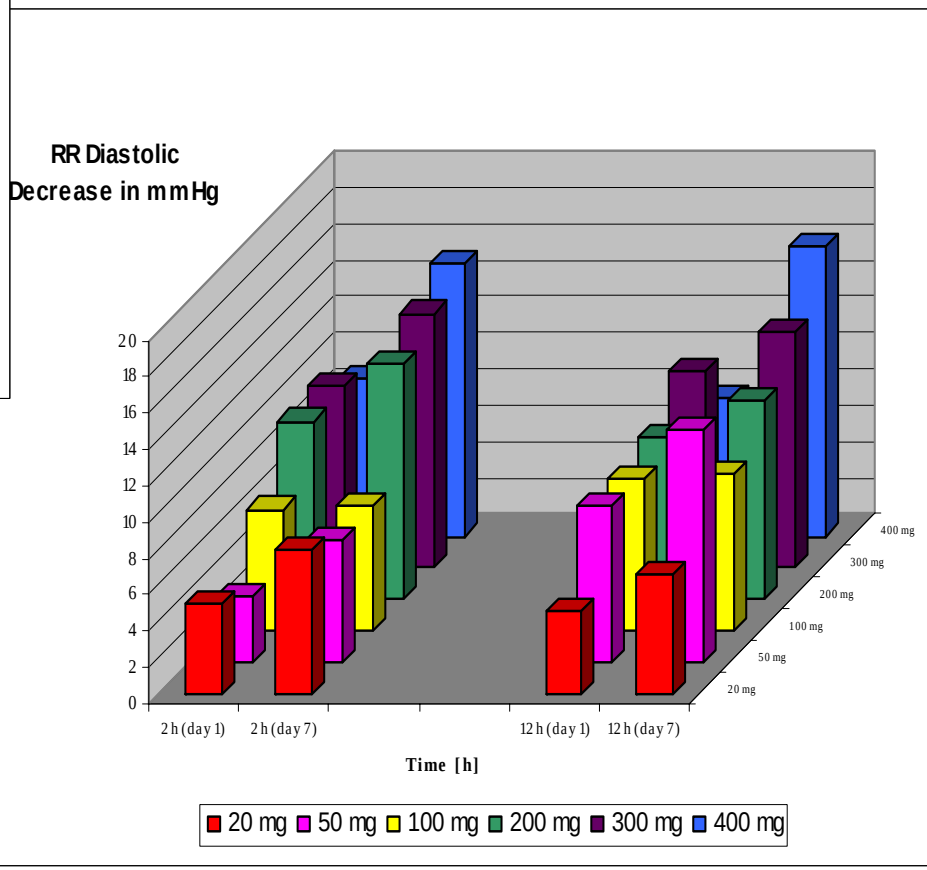


LTD_4 induced bronchoconstriction

MD PoC in Patients - Laboratory and Clinical Marker

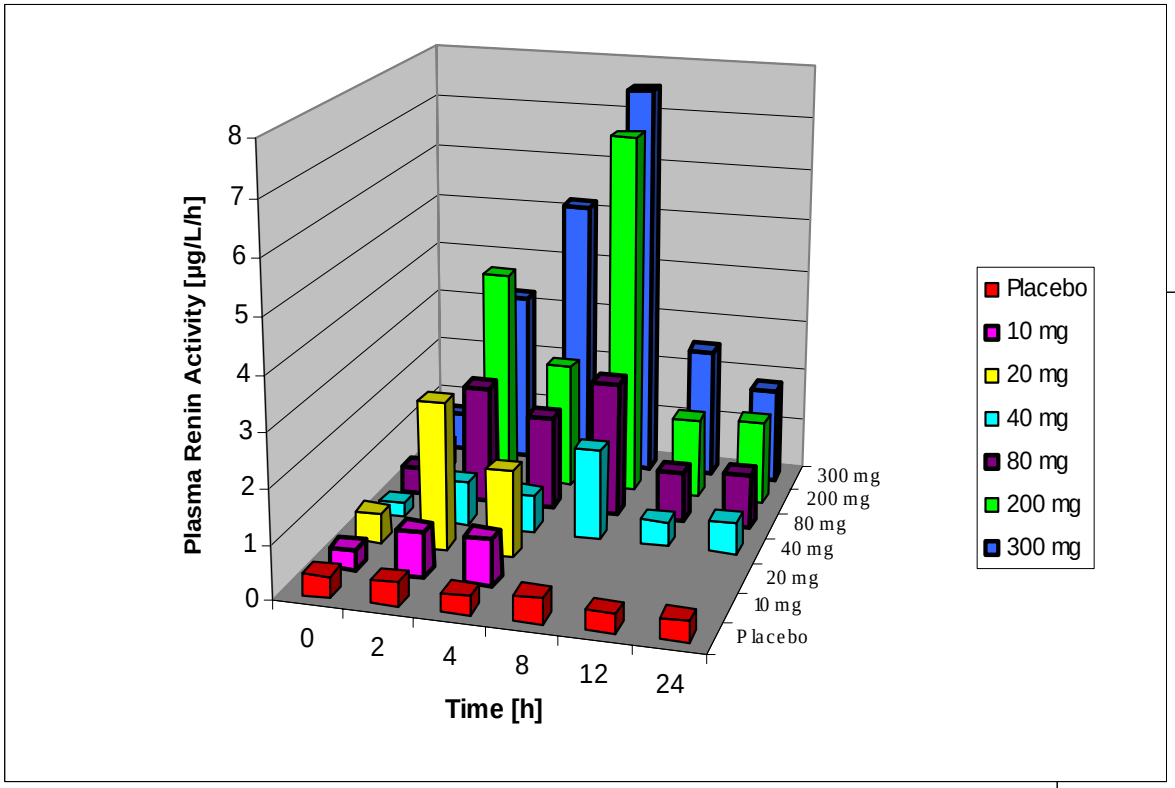


RR Patients



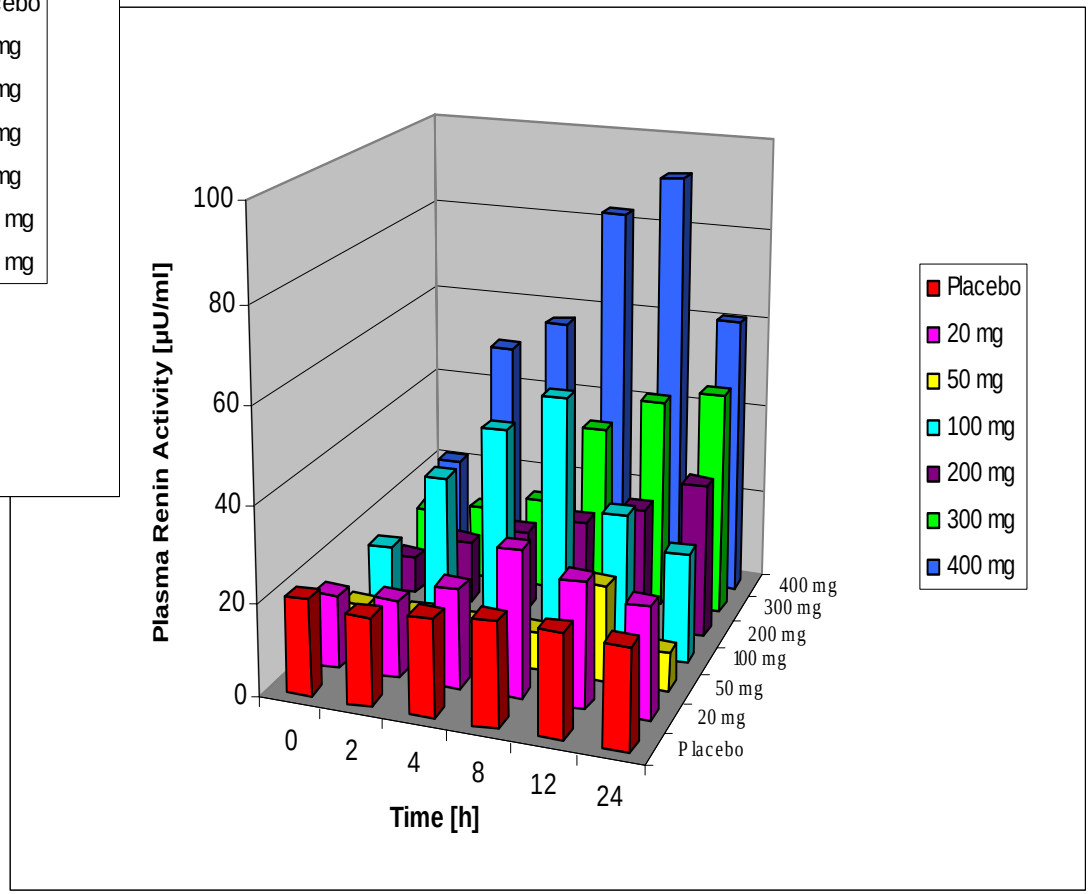
Renin Patients 7d

SD PoM Healthy Volunteers vs Patients - Laboratory Marker



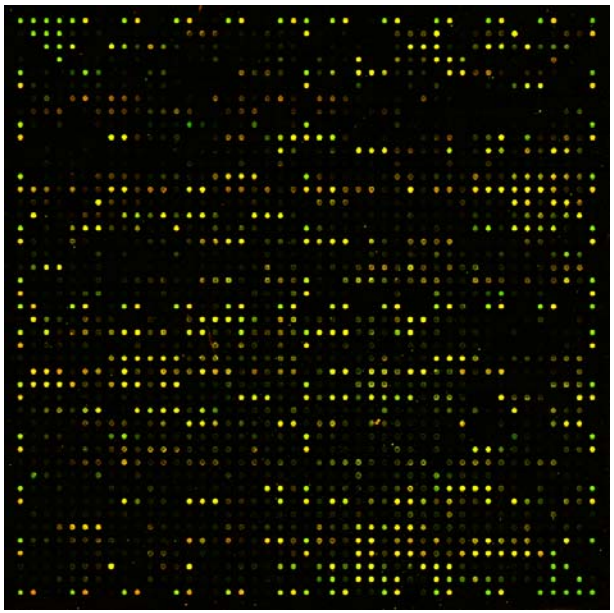
Renin Volunteers

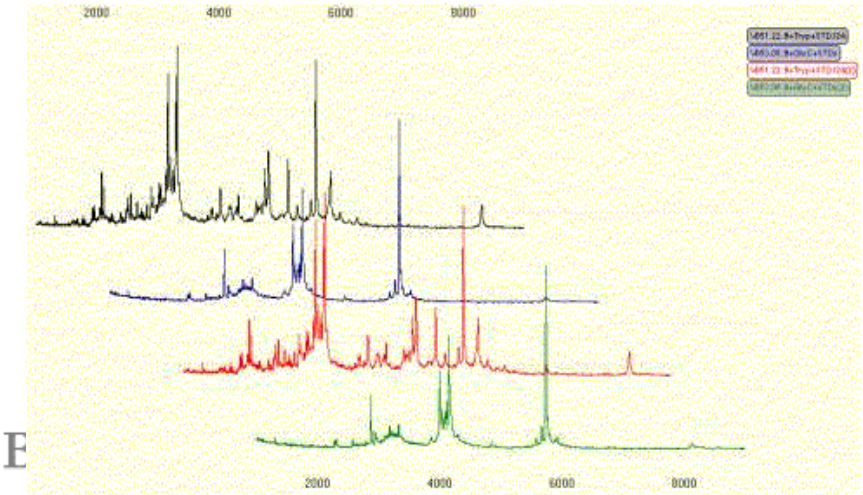
Renin Patients

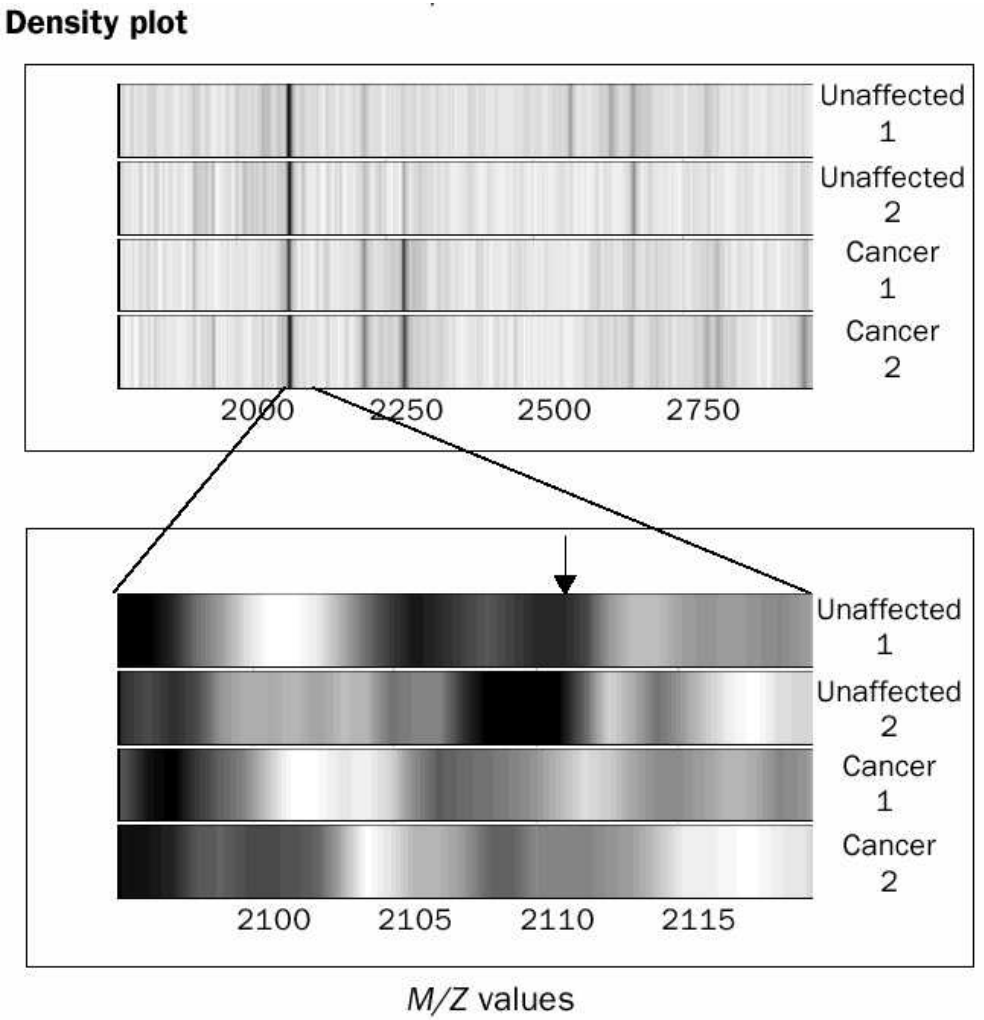


What has changed?

Technology and Knowledge and Degree of Certainty







Other approaches in Early Drug Development

- **Screening IND**
  - **on the basis of existing guidelines**
  - **SD approach alraedy mentioned**
- **Microdosing**
  - **guideline available**
  - **No own experience**
- **Exploratory IND**
  - **exploratory IND (US guideline)**
  - **just released, so far no experience**

Exploratory IND

- **FIM Limited toxicological programme to support**
- **Questions**
  - **Kinetics**
  - **Dynamics**
  - **Candidate selection**
  - **Not to replace MTD**
- **Sd Tox**
- **MD Tox: one species: three doses**
  second species: one dose
- **Starting doses: 1/50 AUC NOAEL rat**

Conclusion

- **FIM studies**
  - **should be indiviualized for every compound and focused on early go/no-go decisions**
- **FIM planning should consider**
  - **early evaluation of new compounds in preclinical phase**
  - **preclinical pharmacokinetic data**
  - **inclusion of biomarkers in FIM studies**
    - **clinical biomarkerslaboratory biomarkers**
      - **pharmacogenetics/genomics**
    - **modelling and simulation**
  - **early realisation of PoM/ PoC**

Basis of Medicine

Primum non nocere