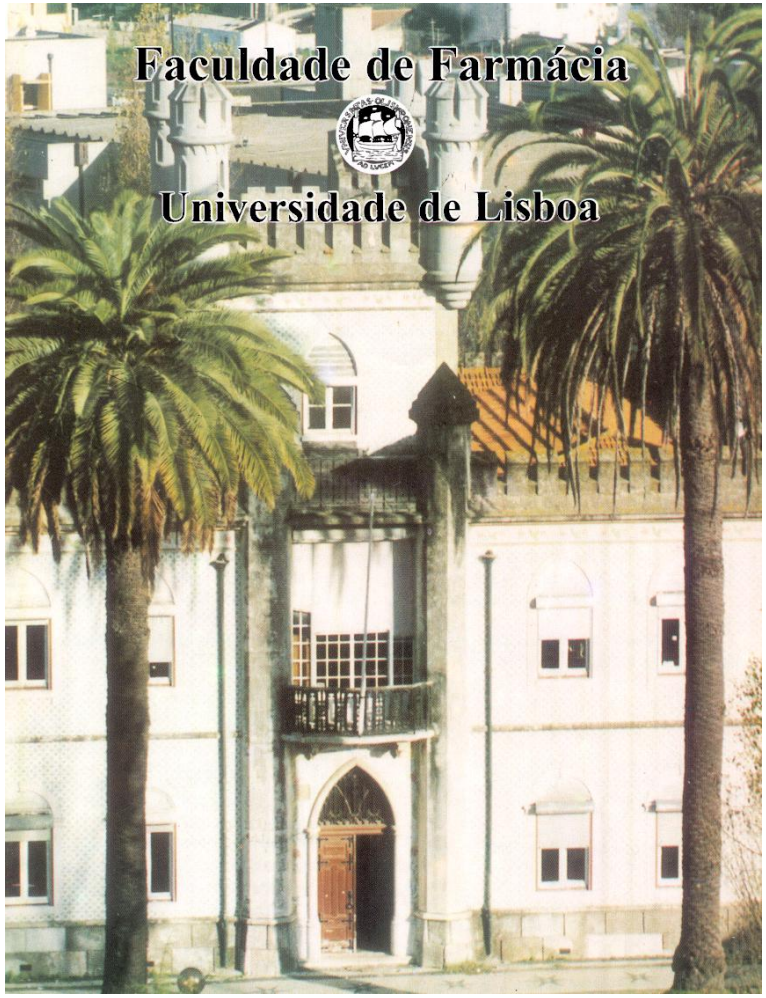
Global Development Challenges: Classical and Advanced Therapy Medicinal products



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iMED, Lisbon University and Infarmed, Portugal
CHMP, CAT, SAWP Member and SWP Chair

NONCLINICAL STUDIES FOR NEW DRUG CANDIDATES

The ultimate aim

Efficiently and effectively justify / support safe introduction in clinical trials & furher progression

- through clinical evaluation
- to registration
- **TO MARKET**

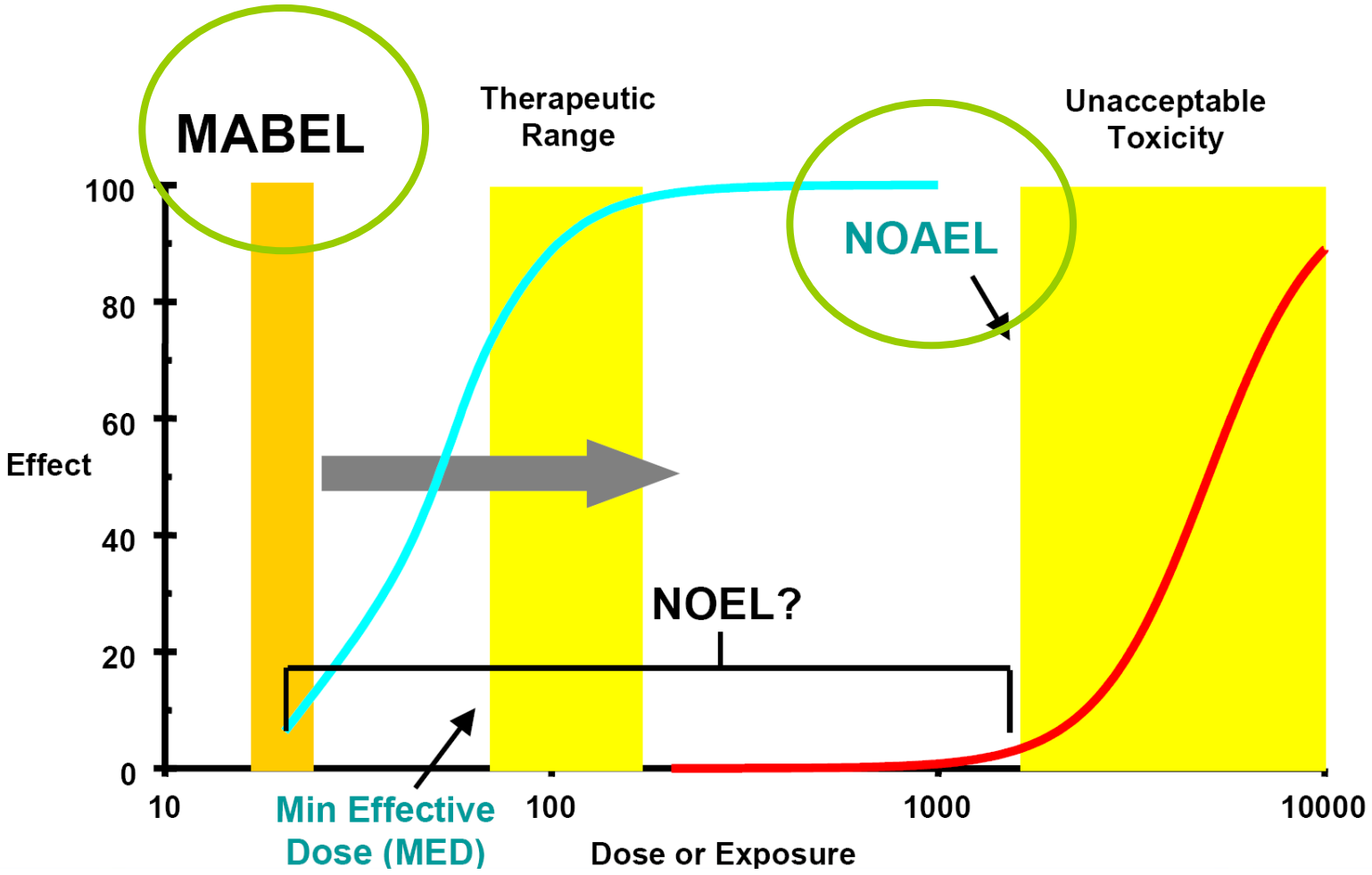
NONCLINICAL STUDIES FOR NEW DRUG CANDIDATES

Supportive Role on Early Clinical Trials

For Decisions on eg

- **FIM dose estimation based on**
  - Pharmacology
  - Safety
    - Safety Pharmacology
    - Toxicology
- **Highlights on safety aspects to monitor**
  - eg liver; CNS; dermal; renal; …
- … … …

FIM: Safe Starting Dose in Man Should Be Driven by Pharmacology & Toxicology



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Subsequent CTs :Stepwise NC program

Adjusted to the Clinical Study

- Subjects

ICH M3; CPMP/ICH/286/95
Under Revision

- Extension of Traget Population

- Disease
  - Incidence
  - severity

The «Core» Nonclinical Package (MA)

- **Pharmacodynamics**
  - Proof of concept
  - Secondary effects
  - Safety Pharmacology
- **Pharmacokinetics**
  - ADME
  - Species selection
  - Human Extrapolation
- **Toxicology**
  - Predictive
  - Mechanistic (?)

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Toxicology

General Toxicity

Superseded by human data

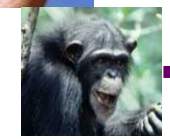
Special Toxicity

NOT *superseded by human data*

Toxicology

Acute Toxicity

Repeated Dose Studies



6 months

2-4 weeks

1 month

3 months

9 (12) months

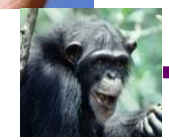
Special Toxicity

NOT superseded by human data

Toxicology

Acute Toxicity

Repeated Dose Studies



6 months

- 2-4 Weeks
- 1 month
- 3 months

9 (12) months

Genotoxicity

- *in vitro*
- *in vivo*

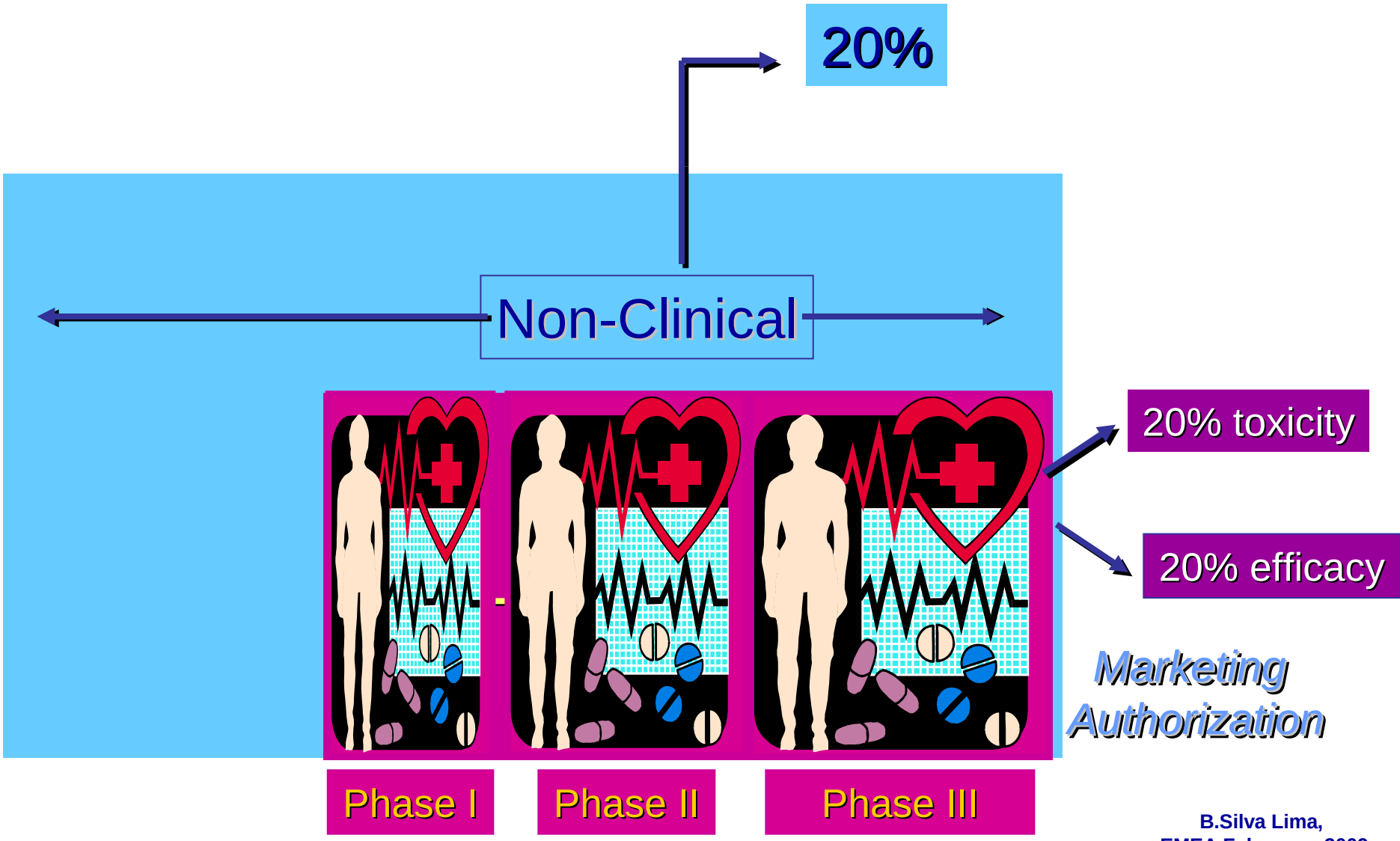
Carcinogenicity

1 life-span
+
1 additional model

Reproduction Toxicology

- fertility
- embryofetal toxicity
- peri-post natal toxicity

Rates & Causes for Drug Failure During Development



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Question for NC and Clinical Scientists

How to Improve?

Main Reasons For (Late) Attrition, in Clinical Trials, eg

- **Poor kinetics** → •Further In silico/in vitro ? •Exploratory Clinical Trials?
- **Insufficient efficacy**
- **Unpredicted safety aspects**

→ •Role for PhGenetics? •Role for Omics? •Role for Biomarkers? •More relevant studies?

ICH M3; CPMP/ICH/286/95

Early-Phase I
(ICH 3 Guideline Ongoing Revison)

PK/PD: microdose studies

Low (PD range) dose studies
better/faster selection
of «promising» molecules?

Adapted
NC package

- Safety pharmacology
- Local tolerance
- Genotoxicity *in vitro*
- Acute Toxicity
- Repeated dose tox. (2W)
  male reproductive organs

Phase I

Some Reasons for Poor Safety Prediction of NC studies

- Development Programs Regulatory – Driven Only
- Innapropriate Study Planning
- Irrelevant Animal Models Used

HOW To “Optimise” Predictivity of NC ?

Small molecules *vs* Biopharmaceuticals *vs* Advanced Therapies

Same General Principles Through Different Strategies

HOW To "Optimise" Predictivity of NC ?

•Use Relevant Species / Models !

- Similar to Human on
  - -Pharmacodynamics
  - -Kinetics (ADME)
  - -Pathophysiology
- respecting ethics & animal welfare

Small Molecules

Interspecies similarities on
- •Metabolism
- •Distribution
- •Excretion
- •Pathophysiology

Biologics

- •Sructural similarities
- •Target expression
- •Target Biology
- •Drug-target interaction

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HOW To "Optimise" Predictivity of NC ?

•In Case of Poor/Non-Relevant Species ?

•eg Human specific Metabolite:

•Test Isolate Metabolite?

•… …

•Use Homologue Molecule

•Use Transgenic Model

•…

Small Molecules

Interspecies similarities on
- •Metabolism
- •Distribution
- •Excretion
- •Pathophysiology

Biologics

- •Sructural similarities
- •Target expression
- •Target Biology
- •Drug-target interaction

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HOW To "Optimise" Predictivity of NC ?

- Study Planning

- In Relevant Species/Model
  - age (eg adult vs juvenile animals)
  - Gender
  - Disease status
- Duration (ICH M3)

Administration Schedule (eg anticancer; ICH S9)

- Early identification of need for mechanistic approaches (eg biomarkers) → Human relevance

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Expectations on Nonclinical Program

At the time of filing MAA

- MOST Concerns Should Have Been Addressed and/or Solved/Considered for Risk Management

- Major NC Problems Should NOT exist!

- **IN THE IDEAL DEVELOPMENT!**

Expectations on Nonclinical Program

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Expectations on Nonclinical Program

At the time of filing MAA

- MOST Concerns Should Have Been Addressed and/or Solved/Considered for Risk Management

- Major NC Problems Should NOT exist!

- **IN THE IDEAL DEVELOPMENT!**

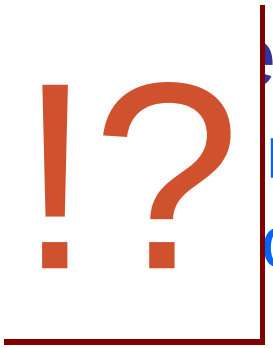
SINCE THE IDEAL DOES NOT EXIST …

Concerns often Persist on eg.

- Carcinogenicity / genotoxicity
- Genotoxic Impurities
- Reproductive Toxicity
- Hepatotoxicity
- …

However, Still Ar ed for MAAs

- Poor justificatic mal models
- Insufficient Kin oxicokinetics



Questioning the Nonclinical Scientists

– Insufficient Nonclinical Programs?

– Nonclinical (Animal) Models Irrelevant?

– Nonclinical Signs Insufficiently Explored?

Too High Expectations for These

To Be Clarified In Clinical Studies?

Summaring: Major NC Challenges

- New mechanisms of action

  -to understand the mode of action (MOA)
  -to pick up PD - related toxicological effects
  -to consider/adapt the MOA in the species used

- Human specific molecules (eg proteins, Abs, ...)

  -use relevant species/model
  -use homologue molecules in the animal species
  -use animal models of the disease
  -use administration schedules and doses mimicking the human situation

- New Therapies/Technologies:(Cells/Biotech/Nano)

  -use of adapted approaches

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Be Aware of
3Rs
&
GMP/GLP/GCP

Thank YOU!

Major Challenges

Take as Starting Point

- Experimental Model
  - carefully chosen,
  - scientifically justif
  - And, if needed, c

Avoid Irrelevar

SEEK FOR I
REGULATC

Be Aware
3Rs
&
GMP/GLP/

Thank YC