Global Development Challenges: Classical and Advanced Therapy Medicinal products

Beatriz Silva Lima
iMED, Lisbon University and Infarmed, Portugal
CHMP, CAT, SAWP Member and SWP Chair
The ultimate aim

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

• through clinical evaluation

• to registration

• TO MARKET
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; …
  - … … …

Supportive Role on Early Clinical Trials

NONCLINICAL STUDIES FOR NEW DRUG CANDIDATES
FIM: Safe Starting Dose in Man Should Be Driven by Pharmacology & Toxicology

[Graph showing dose-effect relationship with MABEL, NOAEL, NOEL, and Med effective dose (MED) highlighting the therapeutic range and unacceptable toxicity areas.]
NONCLINICAL STUDIES FOR NEW DRUG CANDIDATES

Subsequent CTs: Stepwise NC program

Adjusted to the Clinical Study

- Subjects
- Duration of the Study
- Extension of Target Population
- Disease
  - Incidence
  - Severity

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

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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Superseded by human data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NOT superseded by human data
Special Toxicity

NOT superseded by human data

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Rates & Causes for Drug Failure During Development

Non-Clinical

20% toxicity
20% efficacy

Marketing Authorization

Phases:
- Phase I
- Phase II
- Phase III

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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
  - Role for PhGenetics?
  - Role for Omics?
  - Role for Biomarkers?
  - More relevant studies?

- Unpredicted safety aspects

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ICH M3; CPMP/ICH/286/95

Early-Phase I
(ICH 3 Guideline Ongoing Revision)

PK/PD: microdose studies

Adapted NC package

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

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

Phase I

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Some Reasons for Poor Safety Prediction of NC studies

• Development Programs Regulatory – Driven Only

• Inappropriate Study Planning

• Irrelevant Animal Models Used

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HOW To “Optimise” Predictivity of NC?

Small molecules vs Biopharmaceuticals vs Advanced Therapies

Same General Principles Through Different Strategies

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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
- Structural 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?
  • … …

Small Molecules

Interspecies similarities on
• Metabolism
• Distribution
• Excretion
• Pathophysiology

Biologics

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

• Use Homologue Molecule
• Use Transgenic Model
• …

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HOW To “Optimise” Predictivity of NC?

• Study Planning

• In Relevant Species/Model
  • age (e.g., adult vs. juvenile animals)
  • Gender
  • Disease status

• Duration (ICH M3)

Administration Schedule (e.g., anticancer; ICH S9)

• Early identification of need for mechanistic approaches (e.g., 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!
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Concerns often Persist on eg.
- Carcinogenicity / genotoxicity
- Genotoxic Impurities
- Reproductive Toxicity
- Hepatotoxicity
- …

However, Still Are Contended for MAAs
- Poor justification of animal models
- Insufficient Kinetic toxicokinetics
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?

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Summarizing: 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
Be Aware of 3Rs
&
GMP/GLP/GCP

Thank YOU!

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Major Challenges

Take as Starting Point

- Experimental Models and Plans for NC Studies
  - carefully chosen,
  - scientifically justified
  - And, if needed, case-driven.

Avoid Irrelevant Nonclinical Studies

SEEK FOR EARLY ADVICE BY REGULATORY AUTHORITIES

Be Aware

3Rs & GMP/GLP/

Thank YO