

Model-based approaches and decision making in drug development

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'From data to decision: Clinical Reality

*We've got a new wonder drug!
- We give it to you and wonder what it will do'*



Phase II failures: 2008 – 2010

Phase II success has fallen from 28% (2006–2007) to 18% (2008–2009).

As the current likelihood of a drug successfully progressing through Phase III to launch is 50% (Nature Rev. Drug Discov. 10, 87; 2011), the overall attrition of late-stage drug development seems to be unsustainably high.

Nature Drug Discovery, May 2011

Business strategies: Mergers, Revised Portfolio

Aetiology: alpha-galactosidase A deficiency.

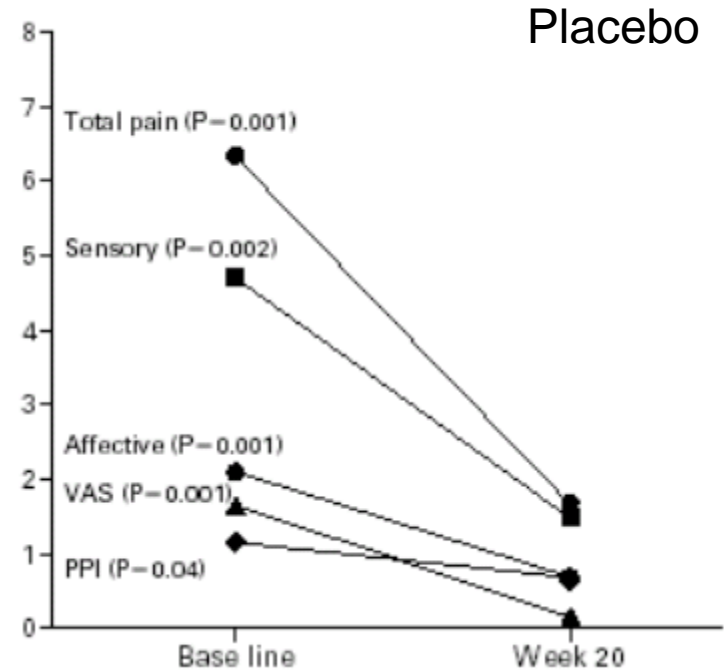
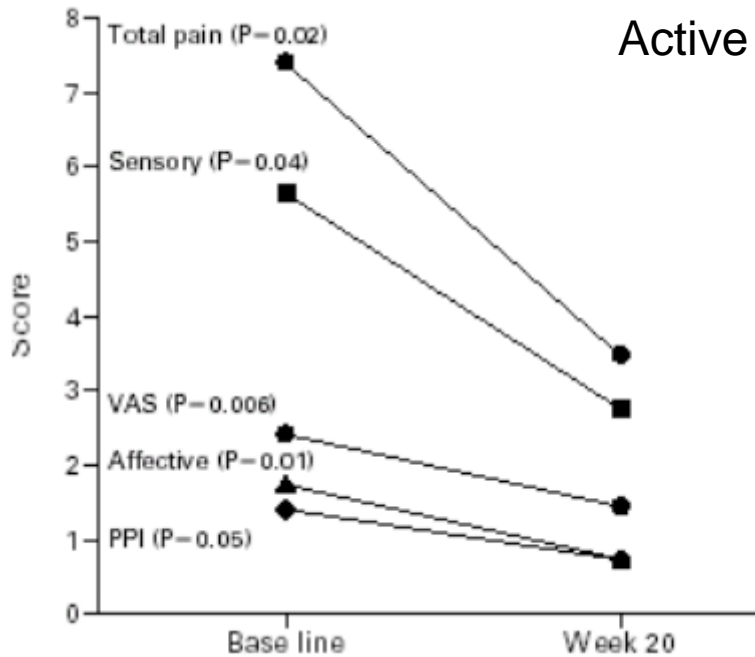
Fabry's disease is a rare X-linked recessive lysosomal storage disease

Fabry's Disease

- ▶ Pain throughout the body
- ▶ Impaired sweating
- ▶ Heat/cold intolerance
- ▶ Skin rashes (angiokeratomas)
- ▶ Corneal whorling
- ▶ Hearing problems
- ▶ Gastrointestinal problems
- ▶ Heart problems
- ▶ Kidney problems
- ▶ Nervous system problems
- ▶ Psychological issues



Large improvement is observed!



Why clinical trials fail?

Target / Pathway

Patient population

Endpoint

Dose rationale

Exposure

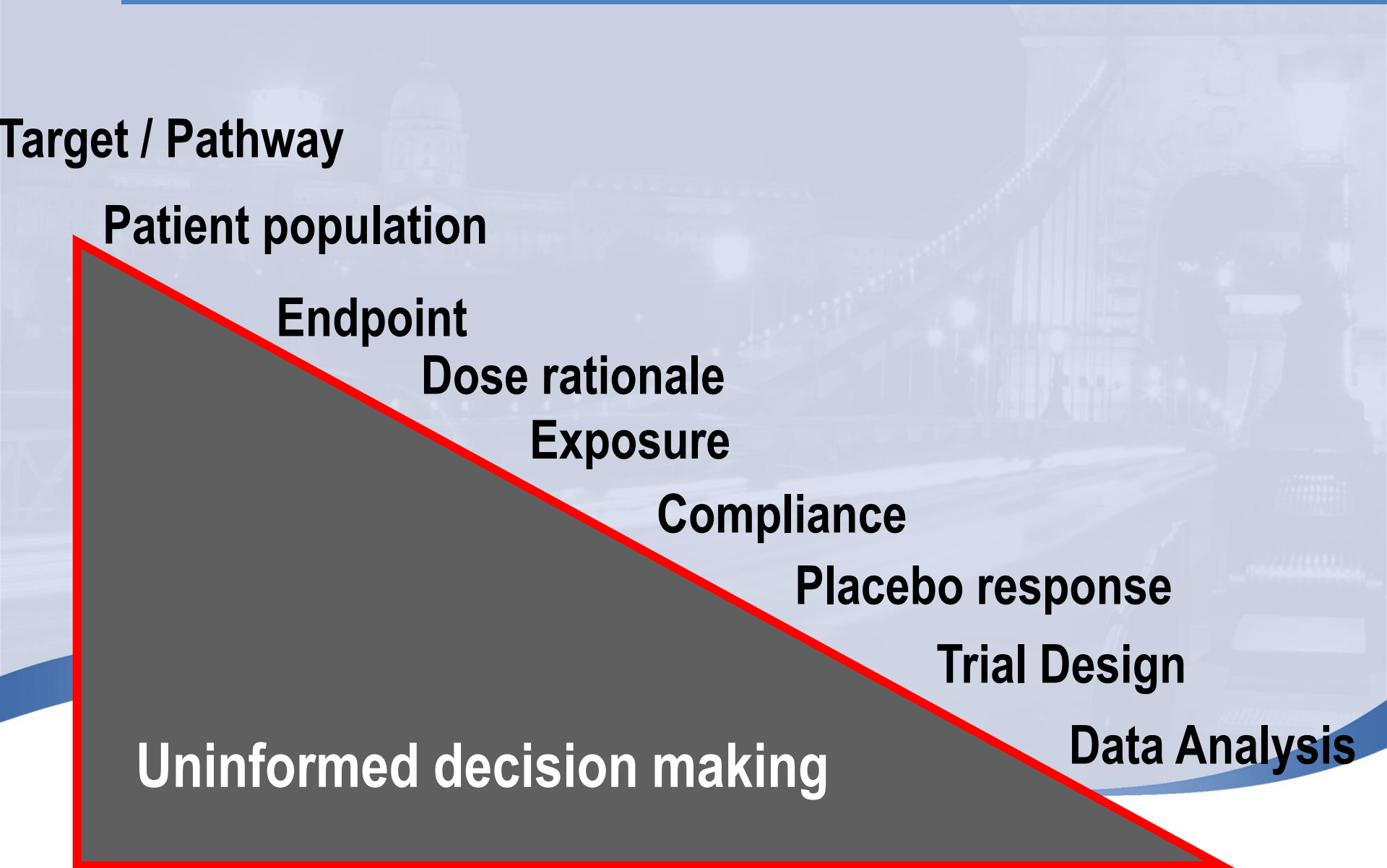
Compliance

Placebo response

Trial Design

Data Analysis

Uninformed decision making



Reasons for Poor Decisions

(Definition: an outcome which should/could have been anticipated)

- Conspiracy of optimism
- Framing the problem too narrowly
- Not involving the right people
- Avoiding uncertainty, ignoring risks
- Ignoring information or does not understand
- Assuming no uncertainty in potential outcomes
- Making decision alone

BIAS

Hammond, Keeney, Raiffa. *Smart Choices* Harvard Business School Press, 1999

Which are the three most important decisions in R&D?

1. Have I selected the right target(s)?
2. Have I selected the right candidate molecule?
3. Have I selected the right dose range for the intended patient population?

Informed Decision and Information Load

Individuals are often unable to deal systematically with large amounts of information, and employ heuristics to reduce the processing required. These often result in decisions being made from the 'context' rather than the 'content' of the information.

Approaches to Decision-Making in Drug Development

Belief is the psychological state in which an individual is convinced of the truth of a proposition. Belief *can* vary between different stakeholders

Evidence is accumulated through observations of phenomena or experiments. Scientific evidence usually goes towards supporting or rejecting a hypothesis. Evidence for an 'effect' within data should be *independent* of the perspective of different stakeholders

Inference is the of deriving a conclusion based solely on what one already knows, often based on the observation of experimental data

We are all prisoners in Plato's Cave

Plato's Cave



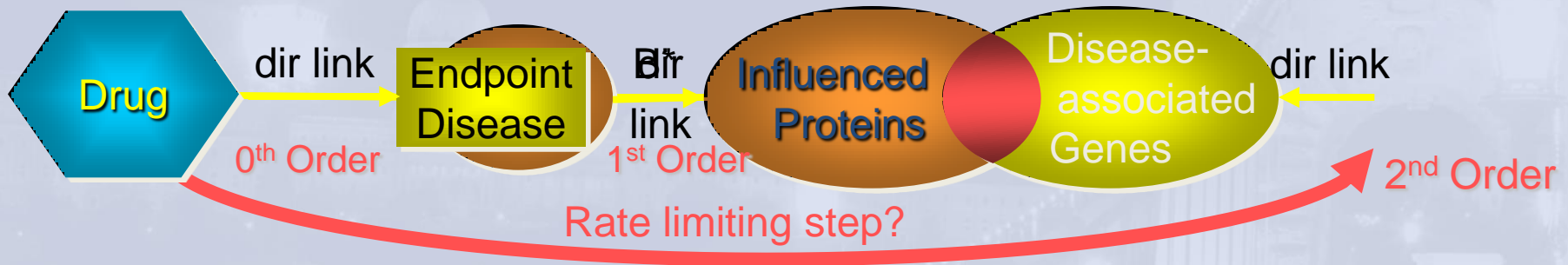
When the prisoners are released, they can turn their heads and see the real objects. Then they realize their error. What can **we** do that is analogous to turning our heads and seeing the causes of the shadows? We can come to grasp the Forms with our minds ... and we do that through statistical inference.

Levels of Complexity in Decision Making

basic – intermediate - complex

- Do decision makers realise the different levels of complexity?
- Do different levels of complexity demand different approaches to ensure “informed” decision-making?
- Decision criteria should be based on /take into account the rate limiting step.

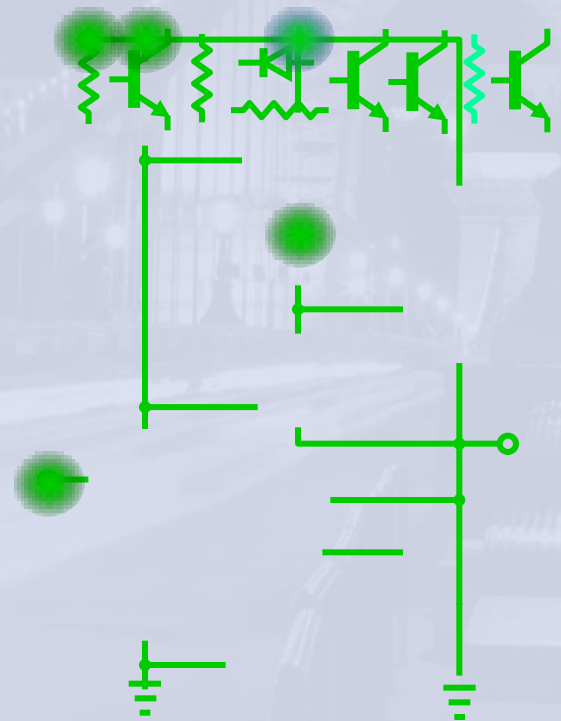
Complexity in the interaction between Drug & Biological System



- “Obvious” input-output relation, system behaviour easy to predict
- The evidence of more *indirect* interactions:
 - The further the link between drug-receptor interaction and endpoint (ie, substrate or functional readout) of disease, the less ‘obvious’ the system behaviour upon different input or levels of drug-receptor interaction

Model-based drug development

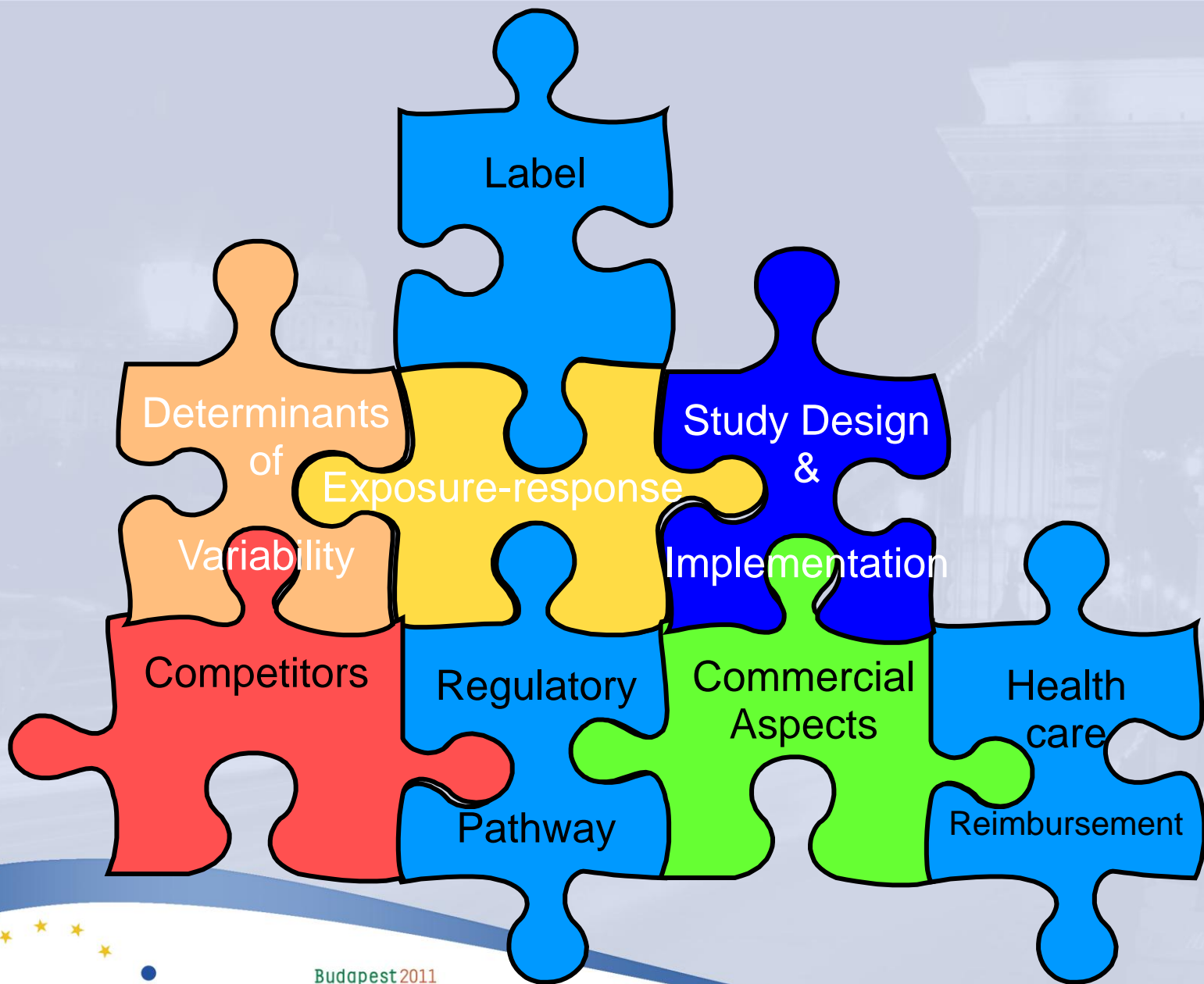
- An appealing and widespread metaphor for **biological systems** such as signalling cascades is that of **electronic circuits**
 - The genome, receptors, mediators physiology, as ‘**parts list**,’ comprises the components
 - Next, we try to understand the connectivity or ‘**wiring diagram**’ of a given system
 - Finally, we want to be able to specify and predict the system’s **dynamic behaviour** and how **experimental design** affects what we observe



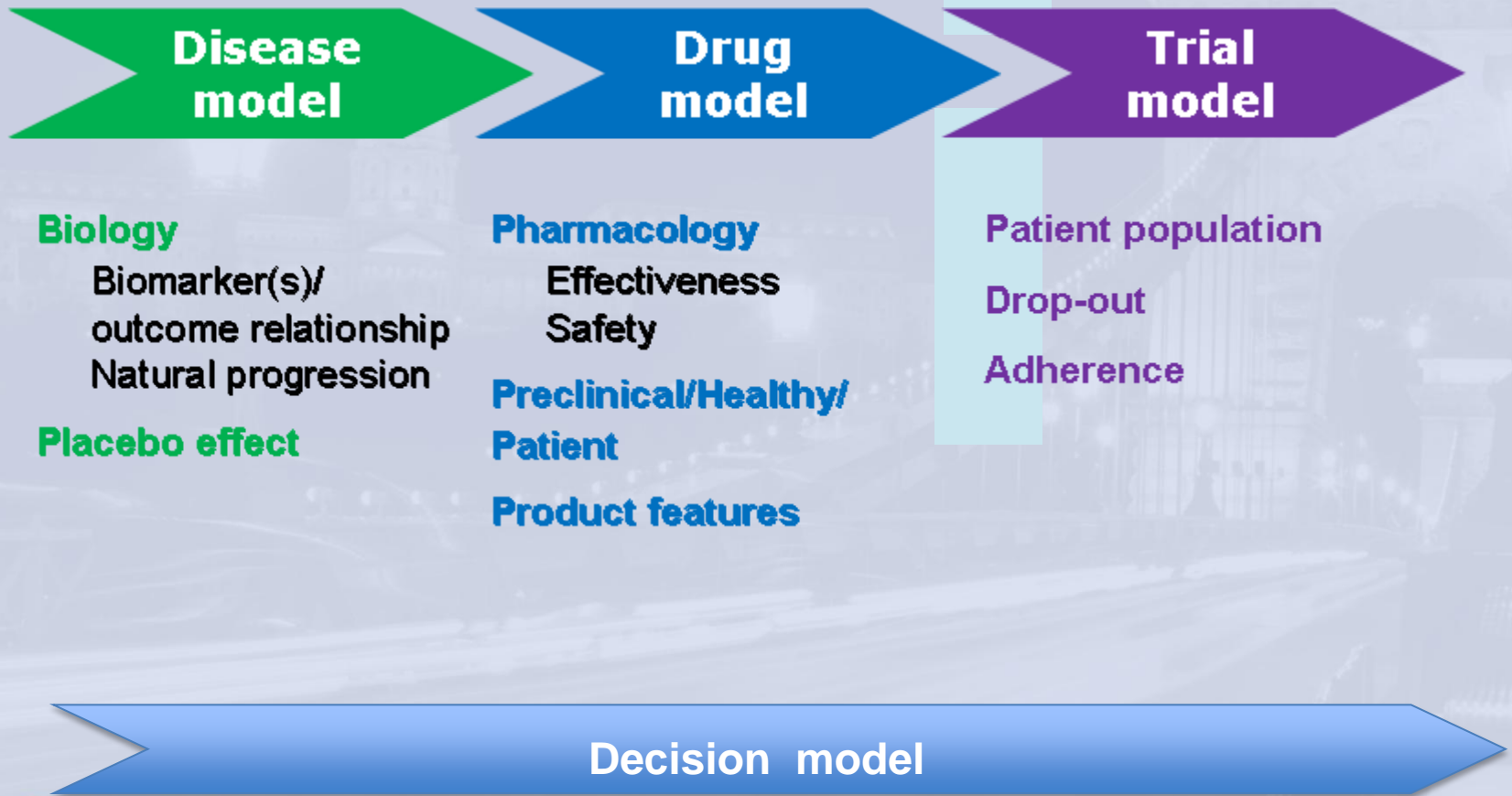
Data is not knowledge!

Modelling as a tool for thinking:

- A model can quantify what you don't know
- A model can help you guess more intelligently
- A model can test alternatives
- A model can integrate data from many sources
- A model can quantify why studies fail
- A model can help understand placebo
- A model can help design a study

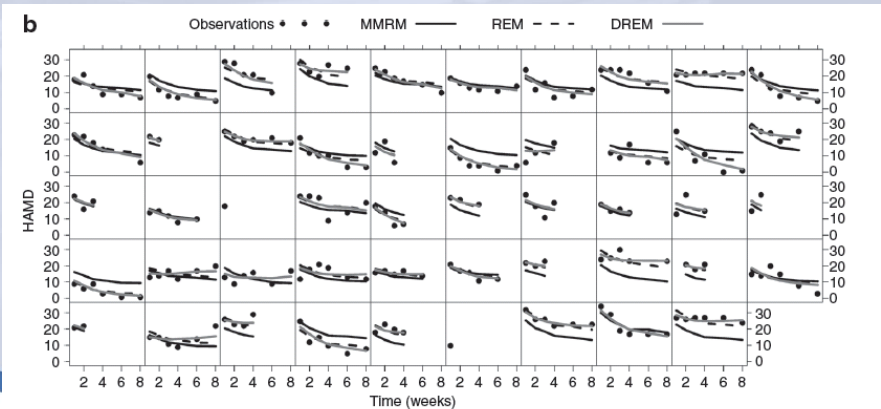
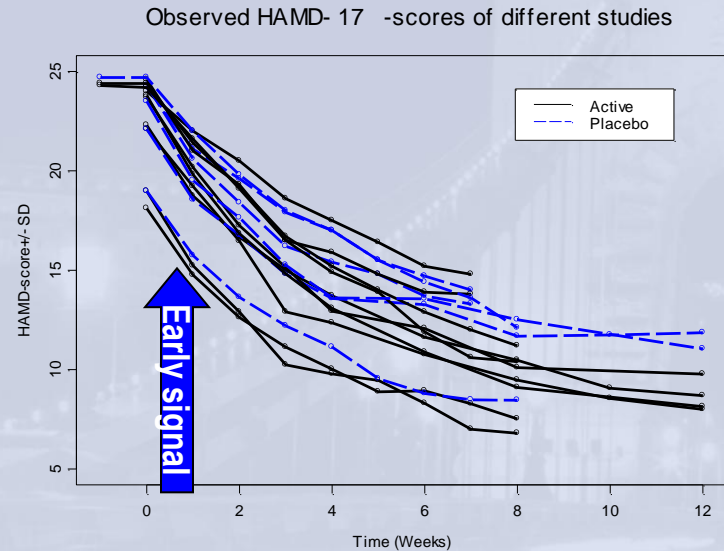


Model-Based Drug Development



Example - Proof of Concept for Antidepressants

- Disease with large placebo response
- Would like to stop trial early for futility
- Historic placebo data included as **prior knowledge**
- Model-based protocol design, including interim analysis with more sensitive endpoint (HAMD subscale)

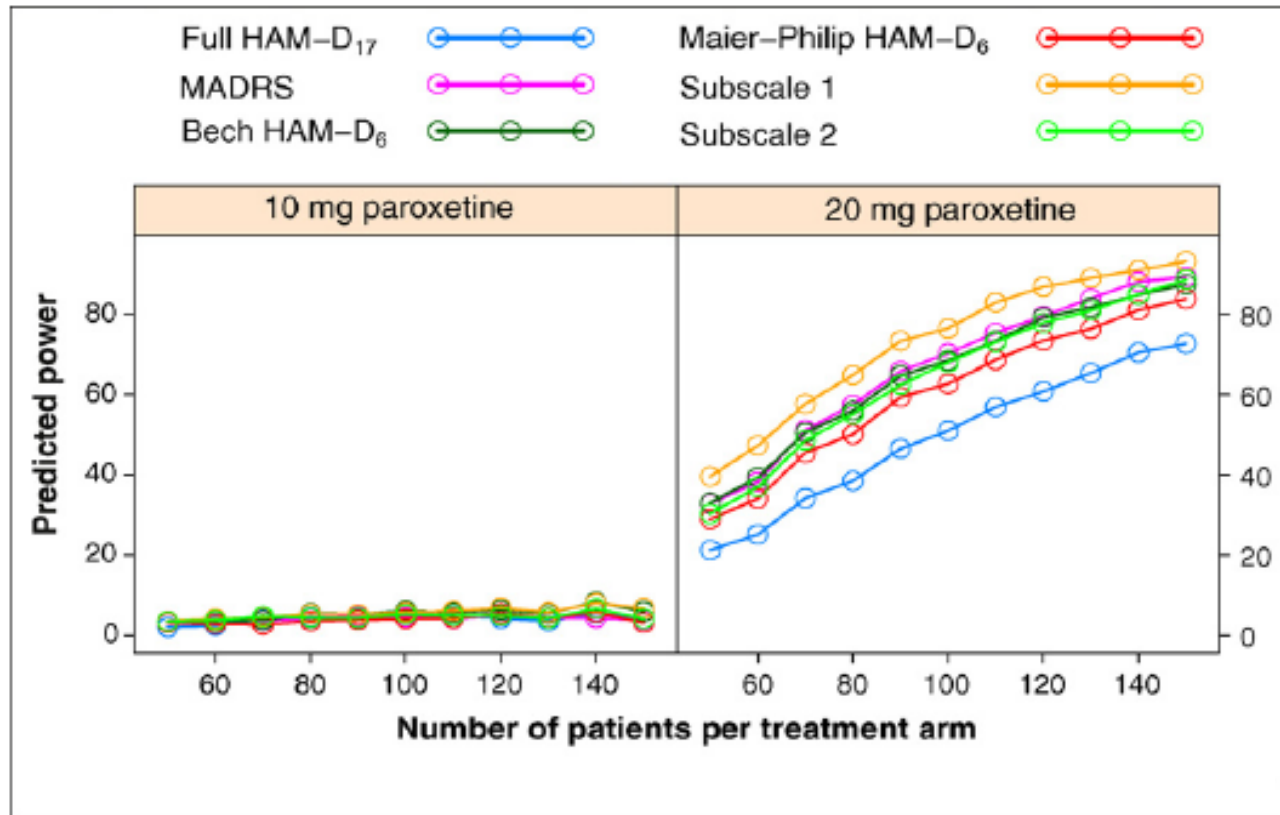


State of the art publication – Clin Pharmacol Ther

From
Part 1
Drug

G Santen¹, E

Clinical trials
of clinical trial



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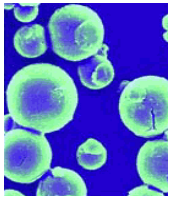
Trials With Antidepressant Drugs

G Santen¹, E van Zwet², P Bettica³, RA Gomeni³, M Danhof¹ and O Della Pasqua^{1,4}

Clinical trials with antidepressant drugs often fail to detect drug effect, even with drugs that are known to be efficacious. In a previous publication, we showed that a model-based approach is required to address some of the existing challenges in the design of clinical trial protocols. Here, we illustrate how the implementation of an interim analysis (IA) may help to

(Model-based) Knowledge Management Platform

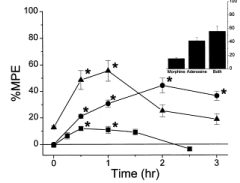
Lead, candidate & product target profile



Pharm Development information profile



External Data & Regulatory Requirements



Clinical information profile



Final "product"



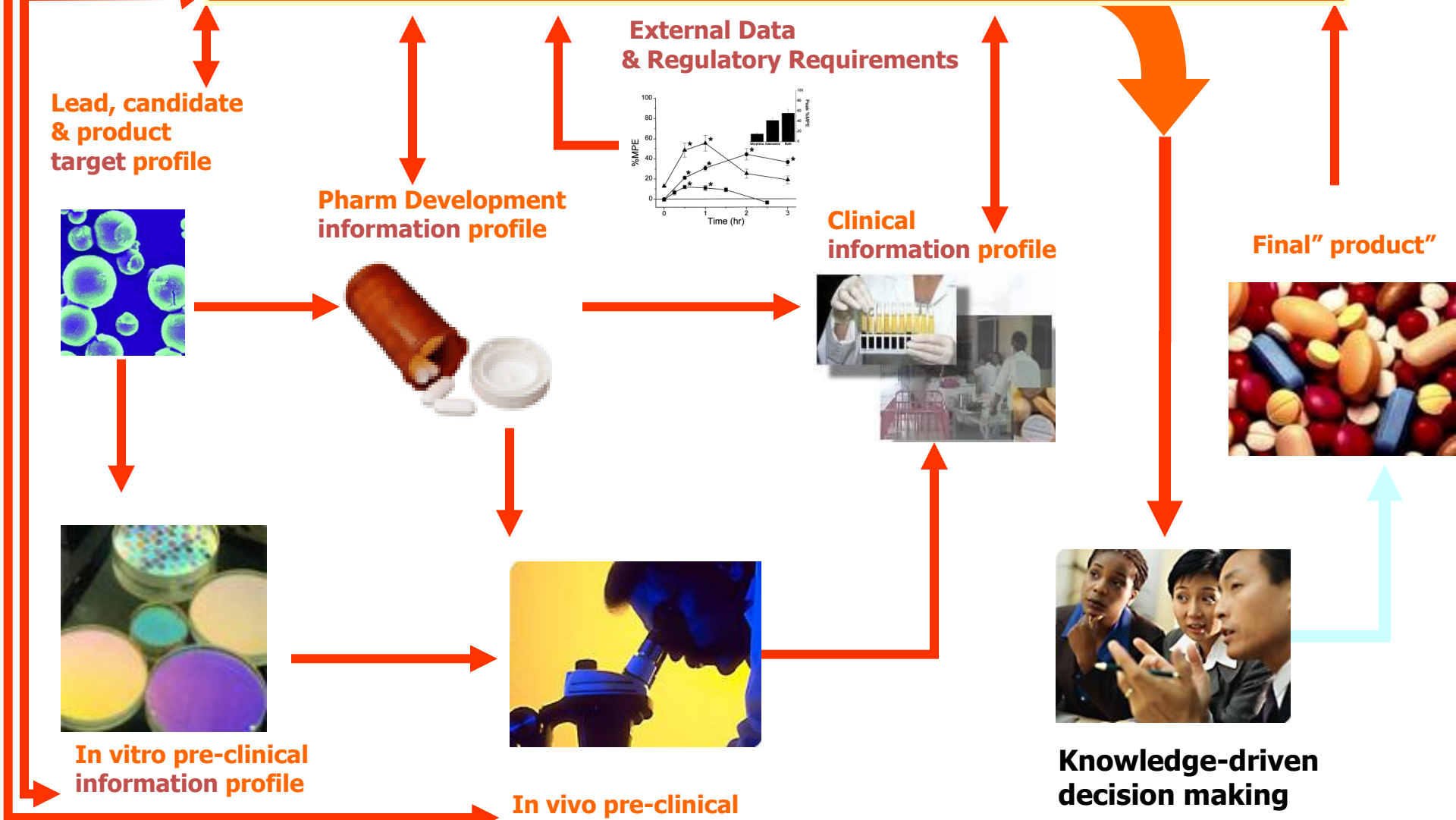
In vitro pre-clinical information profile



In vivo pre-clinical information profile



Knowledge-driven decision making





IN VITRO

IN SILICO

IN VIVO
PRE-CLINICAL

CLINICAL
HEALTHY

CLINICAL
PATIENTS

◆
YES/NO

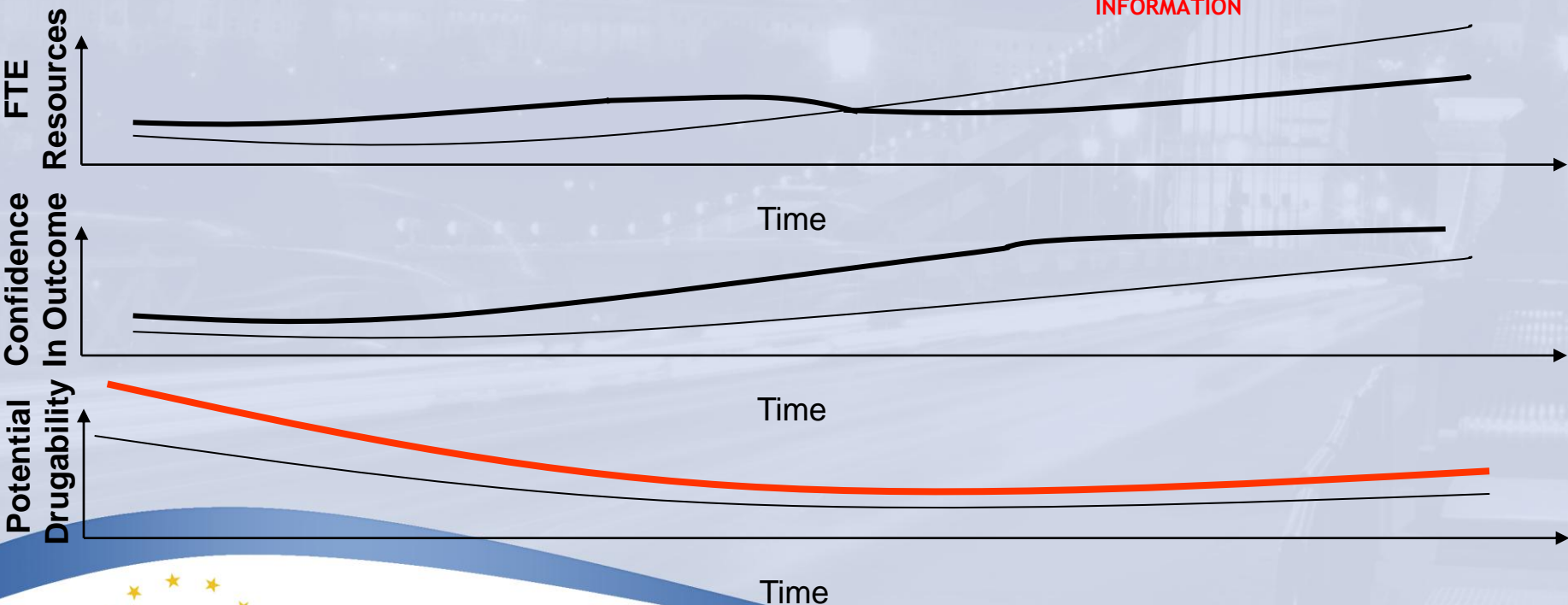
◆
WHICH ONE

◆
HOW MUCH

◆
HOW MUCH
HOW WELL

◆
DETAILED
QUANTITATIVE
INFORMATION

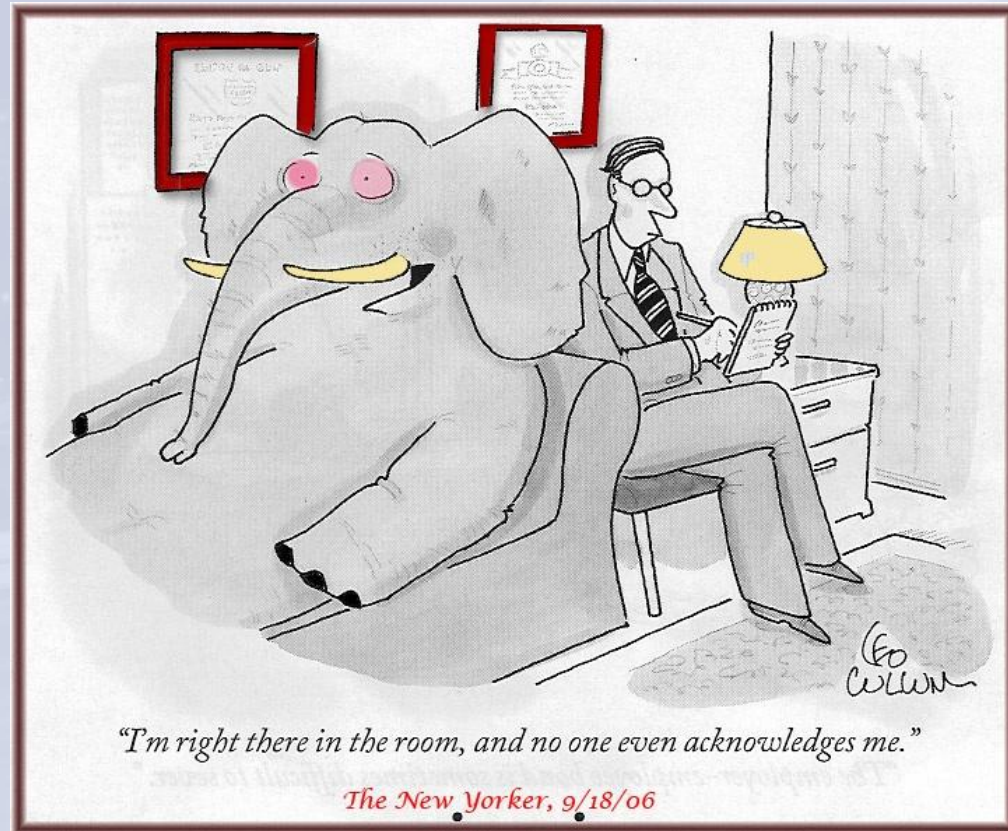
◆
Launch



Summary - Decision making in Drug Development

Informed decision-making is essential to reduce attrition in R&D:

- **integrated developability criteria**
- **appropriate infrastructure and processes**
- **fit-for-purpose experimental protocols, making better use of inferential methods**
- **model-based approach as management tool**



“Learning is not compulsory.... neither is survival”
W. Edwards Deming



“Nothing is more difficult and therefore more precious than being able to decide”

Napoleon Bonaparte