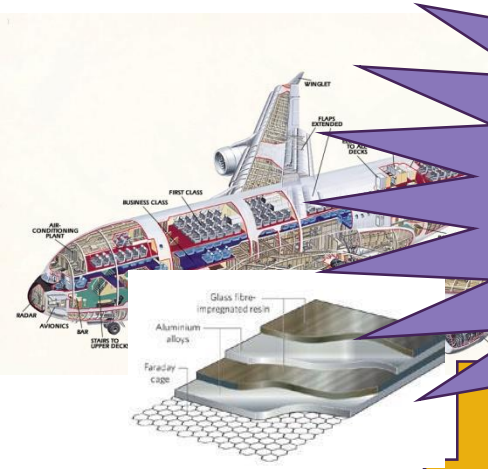
Cross functional M&S

Them

Us

The difference between them and us?



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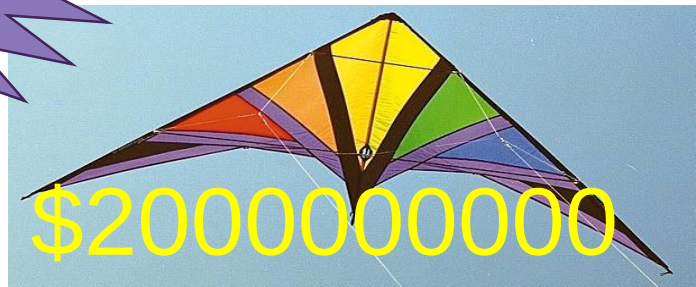
Cross functional Modelling and Simulation



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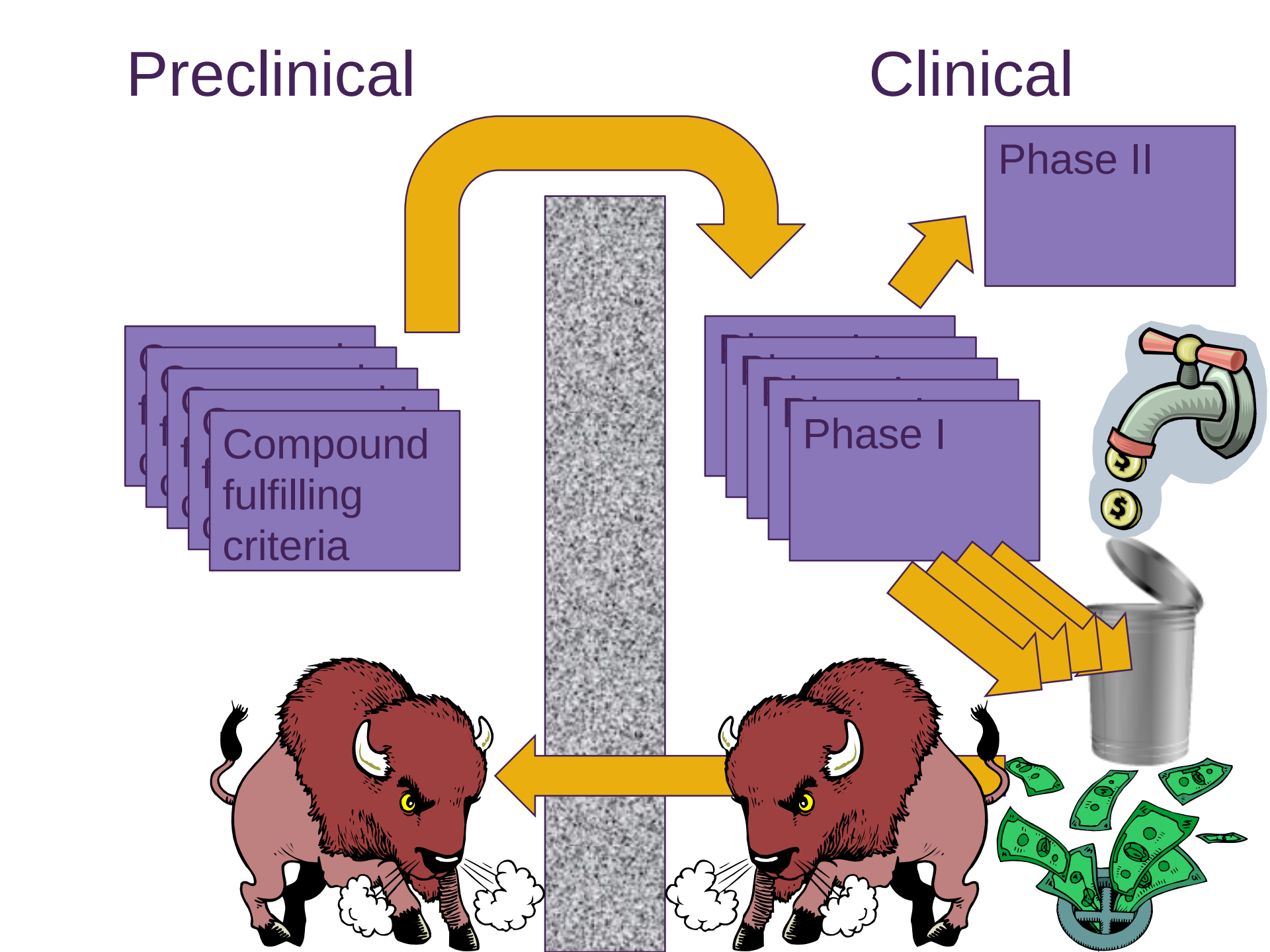

Preclinical
Clinical
Phase II
Compound fulfilling criteria
Phase I

Why is cross-functional cooperation important

Without it human biology, disease and intervention modeling is not possible

Two positive examples

Example 1: unintended cross functional cooperation

- New recombinant drug with a bioavailability of 50% versus animal derived reference
- Drug consisted of several iso-forms
- Drug dosage establish based on animal assay
- Kinetics in animals different from humans
- Receptor affinity different between animals and humans
- Different iso-form have different PK and PD and these are different between animals and humans

- What will this drug do in Phase III

Example 1: unintended cross functional cooperation

- Very tight cooperation between pre-clinical and M&S: real translational medicine 17 years ago
- Some extra pre-clinical experiments

- Prediction of Phase III outcome just prior to top line results were: higher outcome than reference despite relative bioavailability of 50%

- Final study outcome new drug 1.3x as effective

Example 1: unintended cross functional cooperation

- Patent for iso-form composition on outcome
- Feedback to research for new drug specifications
- Ideas on limiting one major SAE with new drug specifications

Example 2: “cross functional cooperation”?

- Different compounds with different affinities to receptor A, B and C in different stages of development
- Several compounds in pre-clinical stage
- Three different possible indications all both chronic and acute
- Phase I and II studies done for all compounds in all indications

- No questions from team

- My question: Can we link receptor affinity ratio to the best indication for that drug

Example 2: “cross functional cooperation”?

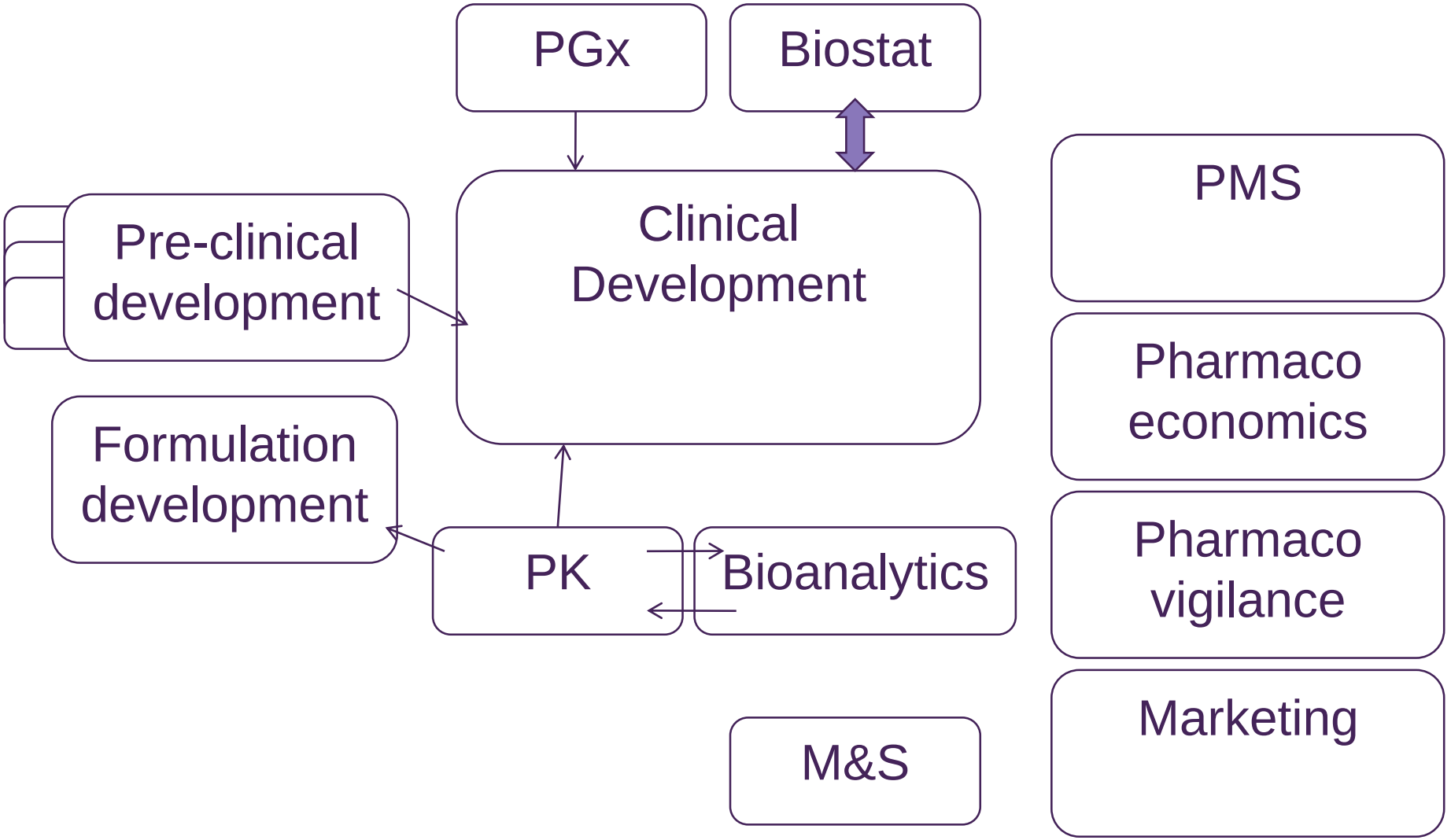
- Almost no cooperation with pre-clinical
- Cumbersome data requisition
- A lot of time needed

Example 2: “cross functional cooperation”?

- A clear correlation of receptor affinity ratio and therapeutic indication
- Prediction for therapeutic area early in development
- Aims for research based on marked need and receptor ratio
- Nothing done with results

- Should have been done earlier and easier

Functions/disciplines involved



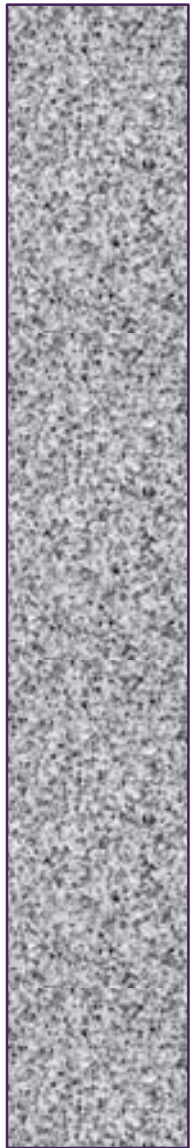
Current practice in M&S

Preclinical PK, PK/PD

Data and models
Person 1
Weight = kg
CRCL using form1

Data and models
Person 2
Wt = gr
RF using form 2

Data and models
Person 3
5 models tried



Clinical M&S

Data and models
Person 4
Weight = kg
CRCL using form1
1000 models tried

Data and models
Person 5
Wt = lb
CL using form 4

Divide and rule

- Or fear from criticism

Changes are needed

- Functional cooperation / M&S team
- Logistics
- Software
- SOP’s

- Change the way of thinking about drug development

Changes are needed

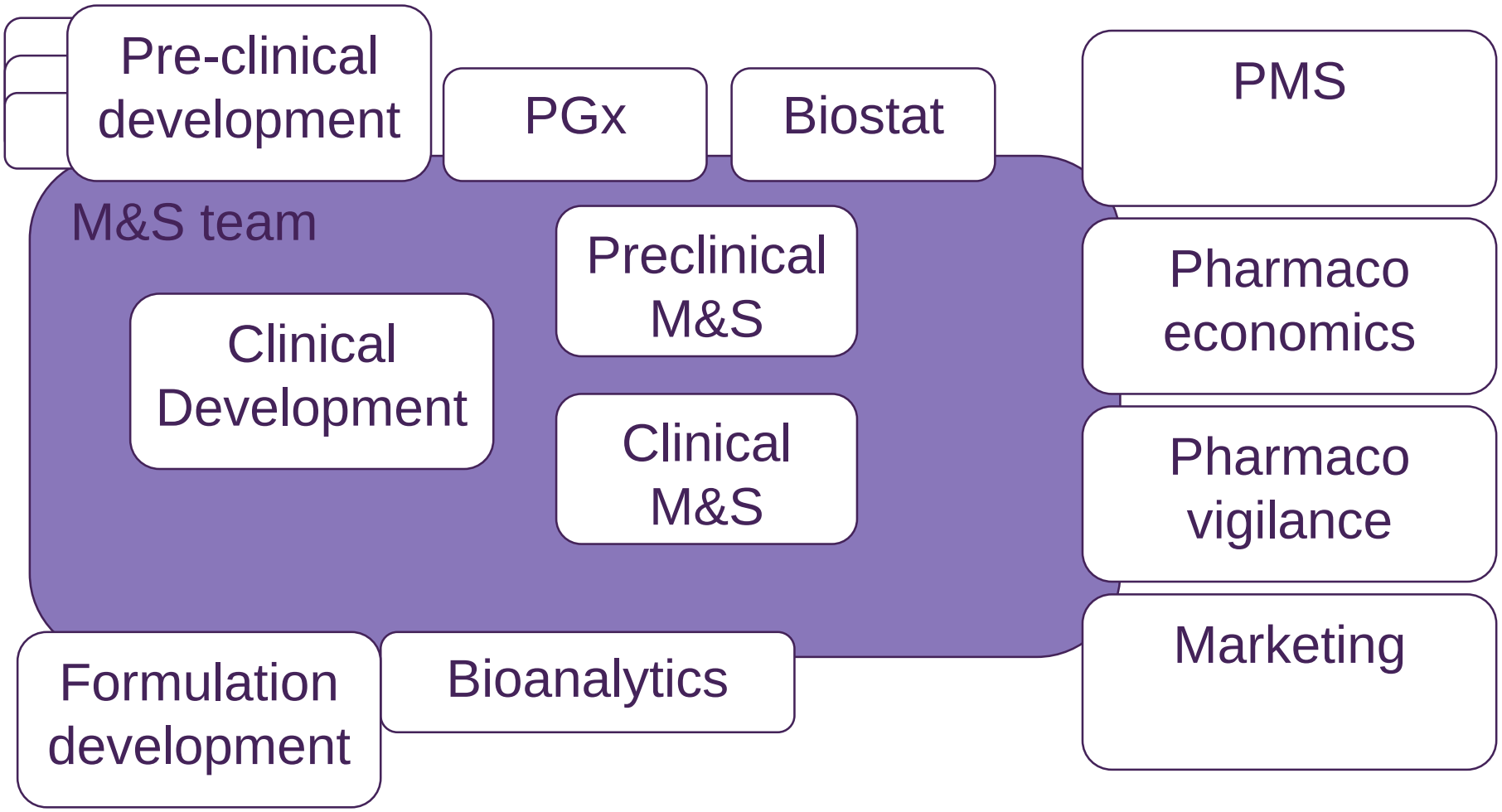
- Software: unified standardized intuitive M&S platform
- Logistics
- Functional cooperation / M&S team
- SOP’s

- Change the way of thinking about drug development

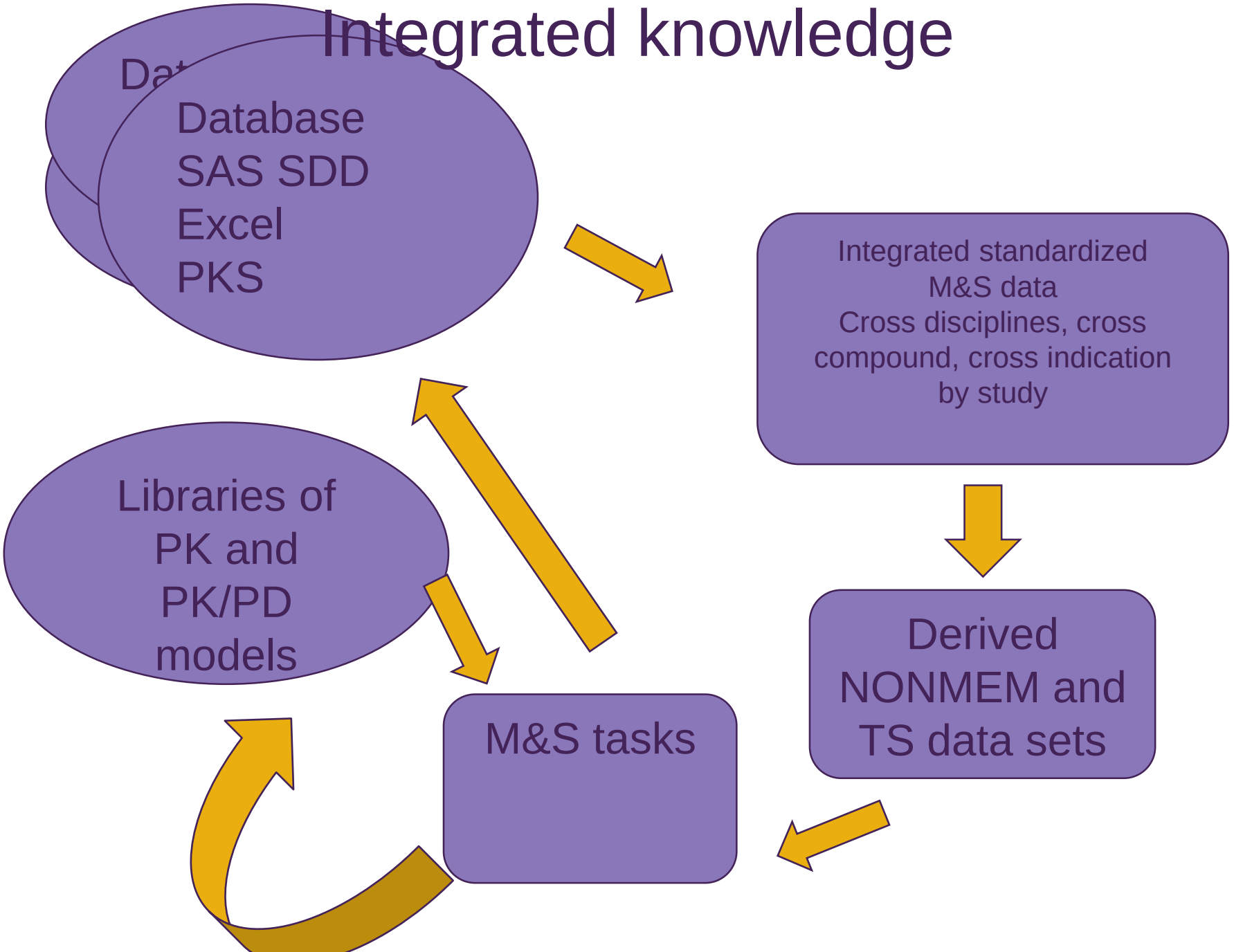
Keep in mind some generalizations

- PK has no relevance for dosing and clinical study design
- Bioanalytics is working as for 100 years; they do not use new possibilities just new machines
- Biostat is needed in Phase III only.
- Most power calculations based on very doubtful background information
- Management just needs a $p<0.05$

Functional changes



Integrated knowledge



Lack of cross functional M&S

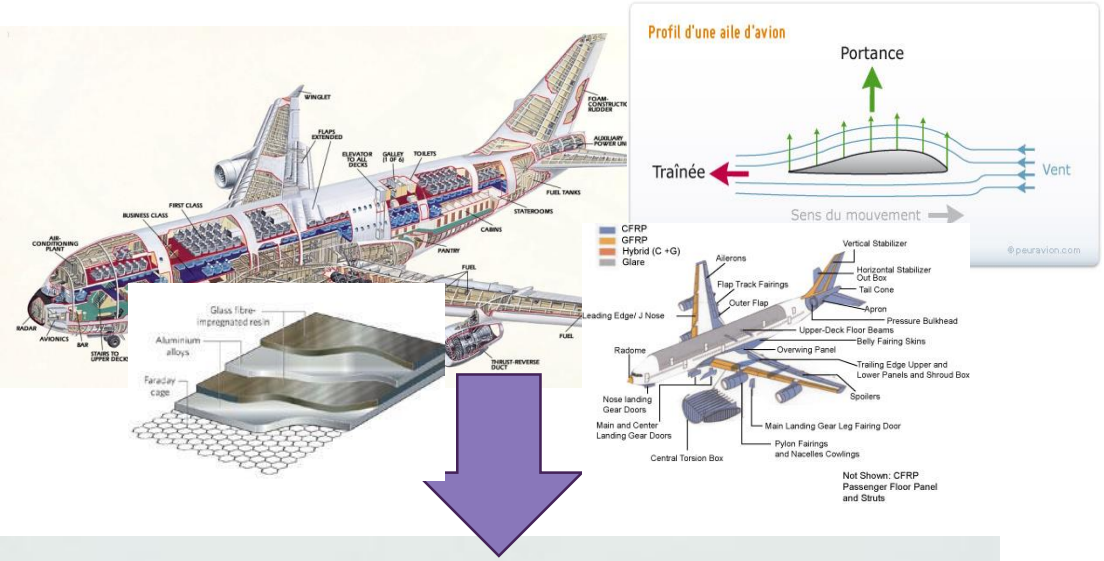
- Less optimal compound selection
- No feedback from findings into R&D
- No advantage of knowledge and lessons learned from other projects

Integrated M&S platform

- Integrated evaluation system
- Transparent model development and published models
- Transparent and standardized data
- Transparent and standardized models
- Up to date libraries of models
- Cloud computing

- Information and models can be easily retrieved
- This will raise discussions and better cooperation
- Coaching made easier
- Acceptance of results increased
- FDA compliant

Them



Us

Patent time ↑

Success rate ↑

Cost ↓

Effect size ↑