Pharmacokinetic modelling and simulation (M&S) – support for drug design and development

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AstraZeneca

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The views expressed in this presentation are the views of the speaker and do not necessarily reflect the views, strategies or policies of AstraZeneca R&D PLC

Myself:

Under grad: Computer System Engineering, BEng (Hons)

University of Warwick

- Control (Prof Keith Godfrey)
- Modelling and Simulation (Dr Mike Chappell)
- Final yr project (collaboration with University of Cardiff, Dr Rachel Harrington and Dr Paul Smith):
  - M&S of uptake kinetics of Topotecan into MCF7 cells
    (Dr Neil Evans, Dr Michael Chappell and Prof Keith Godfrey)

PhD, 3yrs, – School of Pharmacy and Pharmaceutical Science

University of Manchester

- Structural identifiability of PKPD models (Prof Leon Aarons)

Post-doc, 2 yrs CAPKR, Centre of Applied Pharmacokinetic Research

University of Manchester (CAPKR funded by Pfizer, GSK, Novartis, Servier , Eli Lily)

- WBPBPK and other mechanistic modelling (Prof Leon Aarons and Prof Malcolm Rowland)

Clinical Pharmacometrician, AstraZeneca, 4.5 yrs, QCP, ECD, AZ, UK

- Oncology portfolio

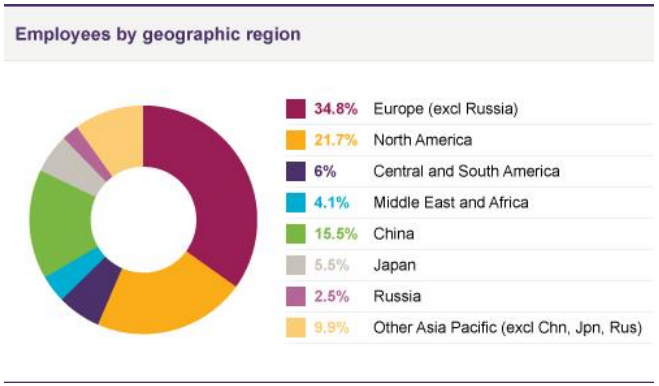
Project Manager and functional representative of AZ Paediatric working group

- Across therapeutic area on paediatric portfolio
- Ensure Clin. Pharm and M&S supports science and regulatory interactions

Pharmacometrics - is the science of developing and applying mathematical and Statistical methods to characterise, understand and predict a drug's pharmacokinetics, pharmacodynamics, and biomarker outcome behaviour.

AstraZeneca - overview

We employ around 51,500 people worldwide: 34.8% in Europe, 21.7% in North America, 6% in Central and South America, 4.1% in the Middle East and Africa and 33.4% in Asia Pacific.



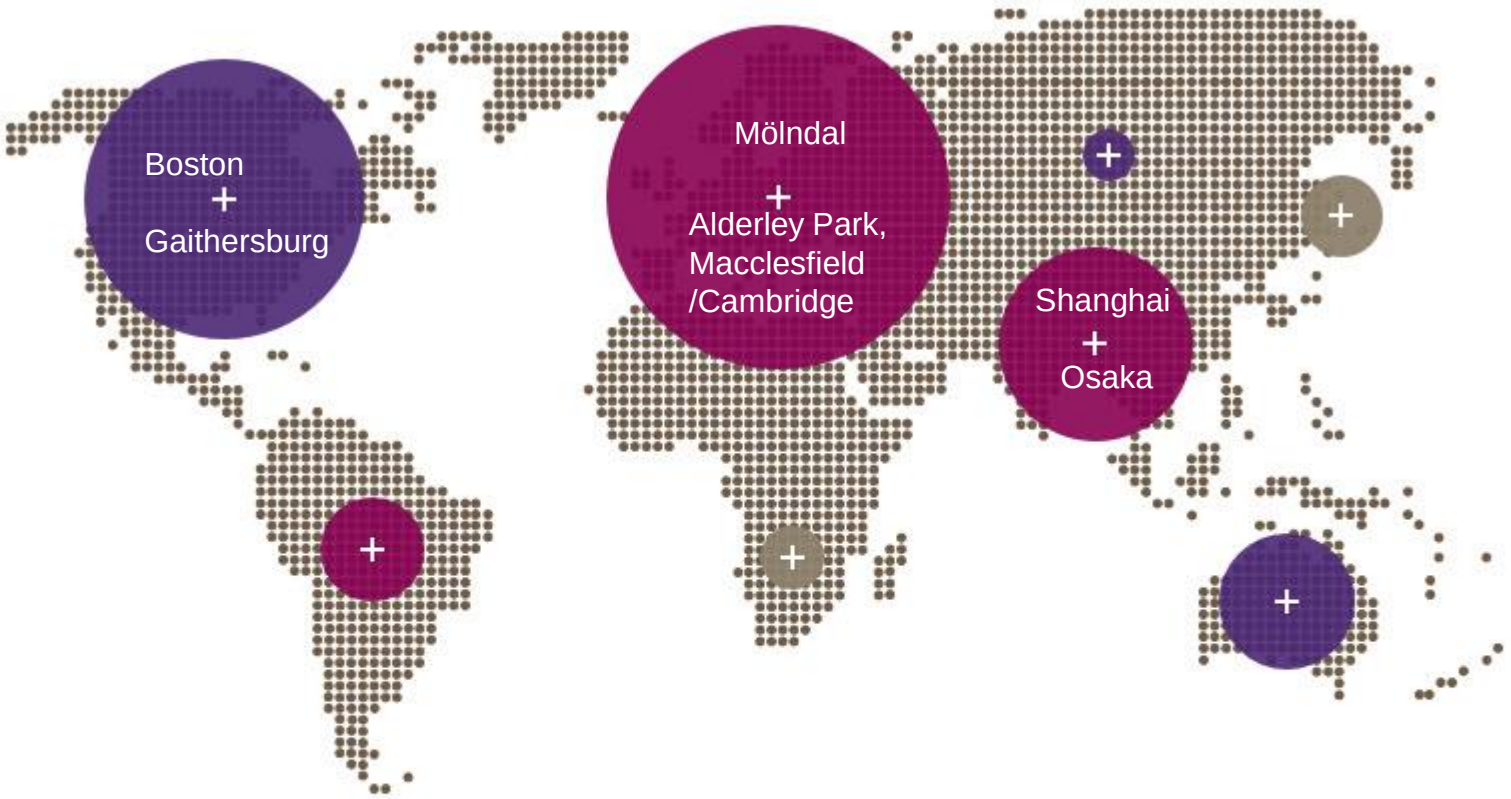
We invest over $4 billion in R&D each year and have over 9,000 people in our R&D organisation

Our primary focus is on three important areas of healthcare: Cardiovascular and Metabolic disease (CVMD); Oncology; and Respiratory, Inflammation and Autoimmunity (RIA). We are also active in the Infection, Neuroscience and Gastrointestinal (ING) disease areas. (both small and large molecules)

We manufacture in 16 countries and are committed to ensuring a reliable supply of medicines where and when they are needed.
We work in over 100 countries and our medicines are used by millions of patients worldwide.

In 2012, our worldwide sales totalled $25.7billion

Global R&D Sites



51,500* employees worldwide

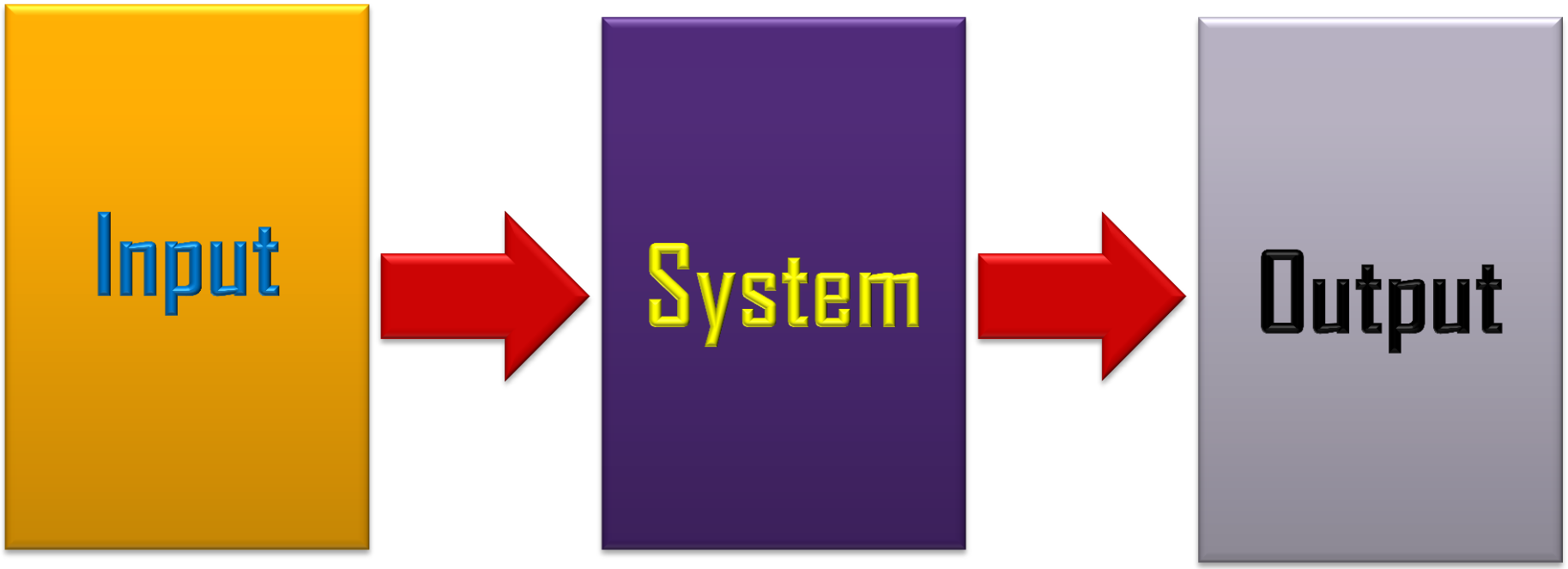
9,000* employees work in R&D

29,600* employees work in Sales and Marketing

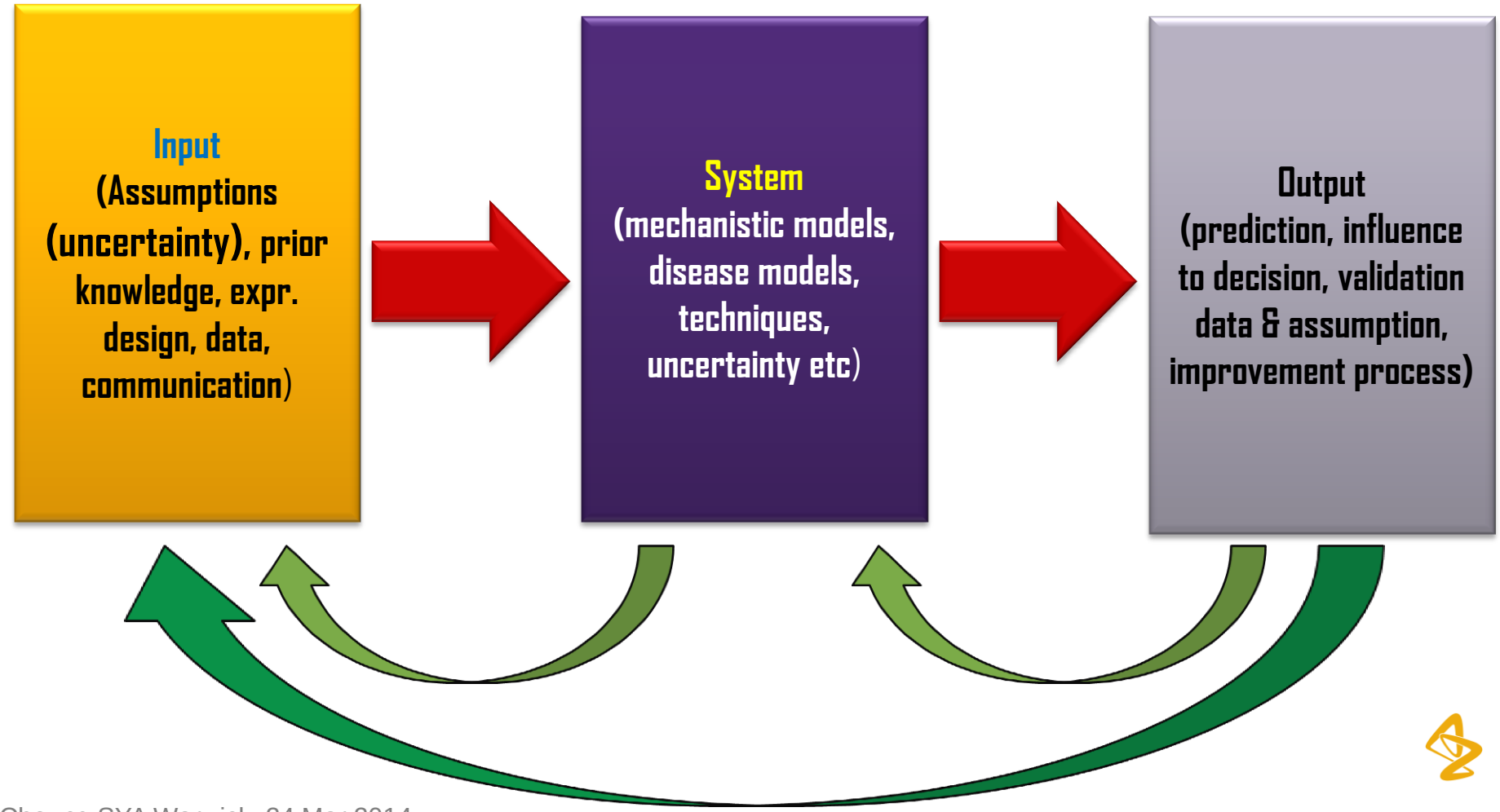
8,700* employees work in Supply and Manufacturing

What can modelling and simulation provide for drug development?

From an engineering point of view:



From an engineering point of view:



Terminology, quick brief overview:

Pharmacokinetics (PK) :

What the body does to the drug, ADME, absorption, distribution, metabolism and elimination/excretion

- Covers:
  - route of administration: oral, iv, bolus, inhaled etc
  - Measurements: serum, blood, plasma, urine, breath etc for drug concentration

Pharmacodynamics (PD):

What the drug does to the body, physiological effect and response of the body to the drug agent/s

- Covers:
  - blood pressure, liver function, glucose, insulin, fat cells etc

Clinical outcome:

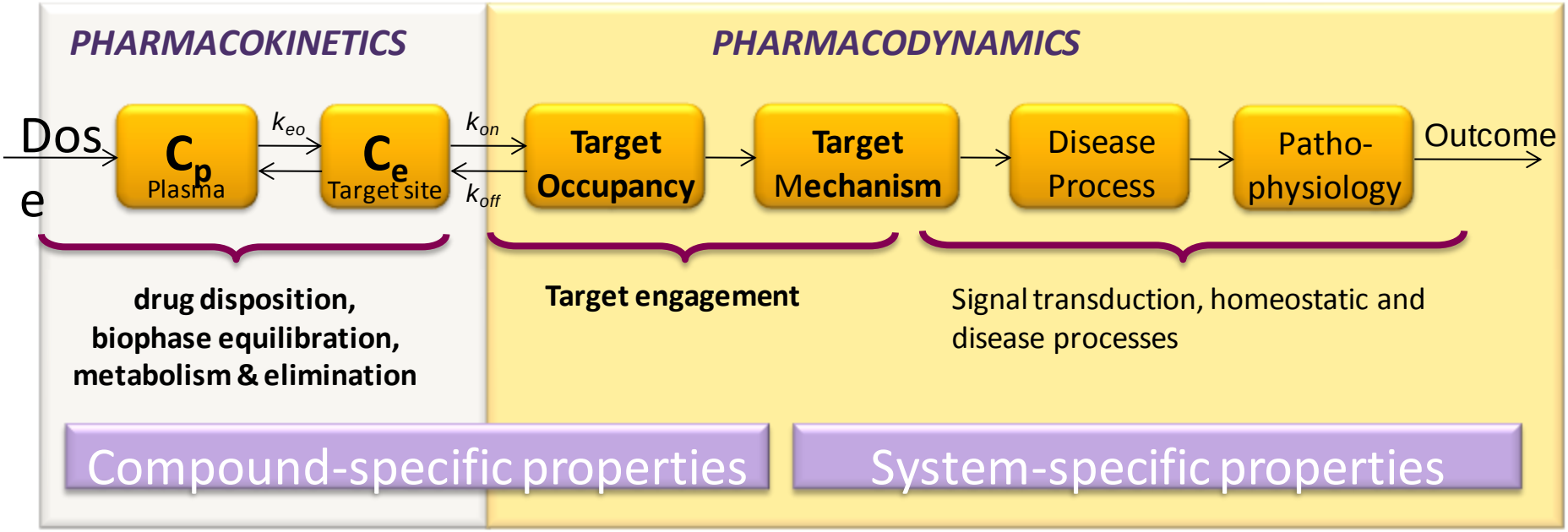
- Covers:
  - survival, adverse effect, image scan (tumour size), bone density, weight lose, pain etc

Biomarker (BDWG):

A characteristic that is objectively measured and evaluated as an indicator of normal biological process, pathogenic process or pharmacologic responses to a therapeutic intervention. (A lot of time, we use surrogate endpoints, a biomarker to sub for clinical endpoints)

- Blood pressure, body temperature (for paracetamol) etc

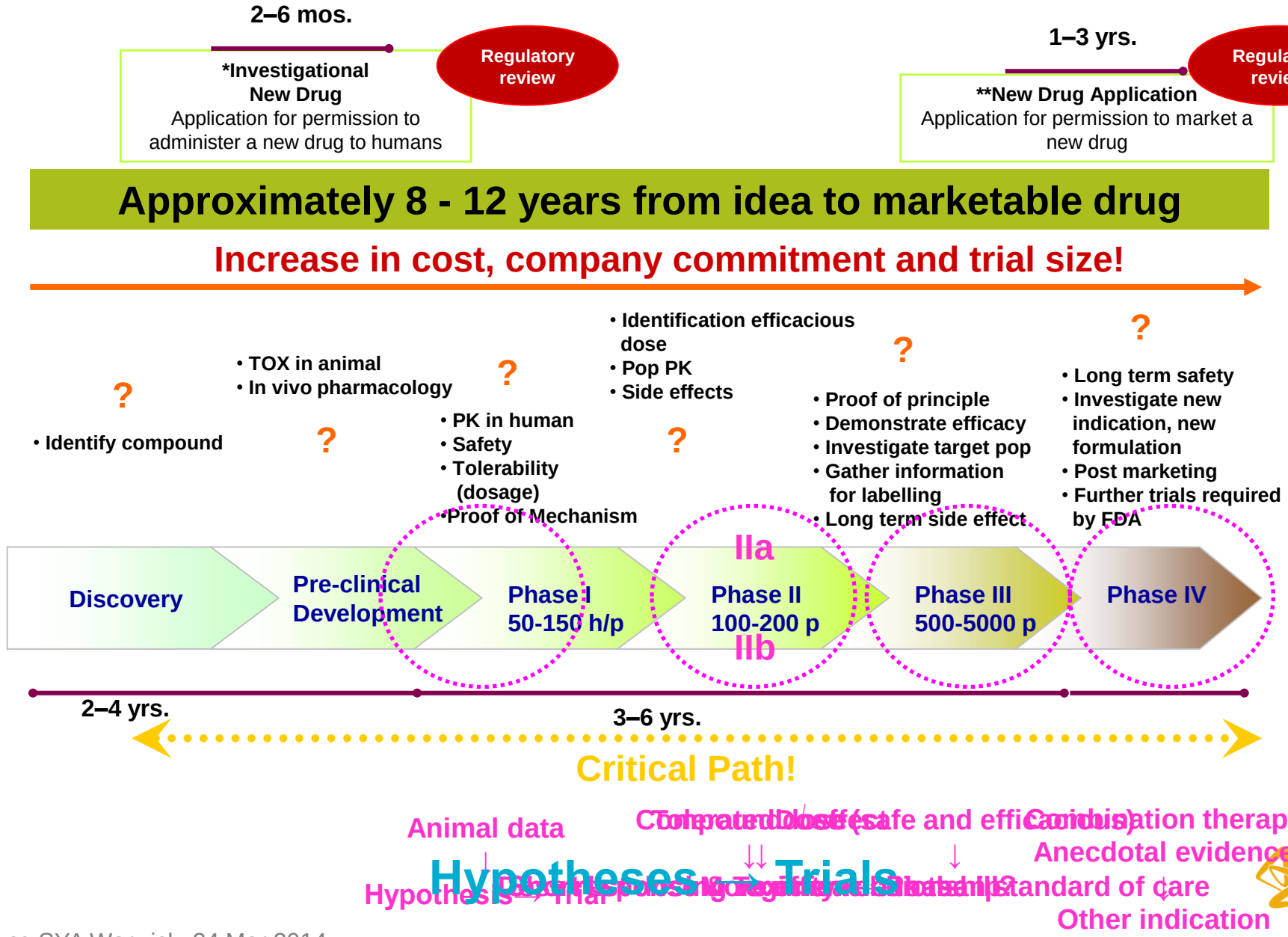
Pharmacokinetic-Pharmacodynamic Principles

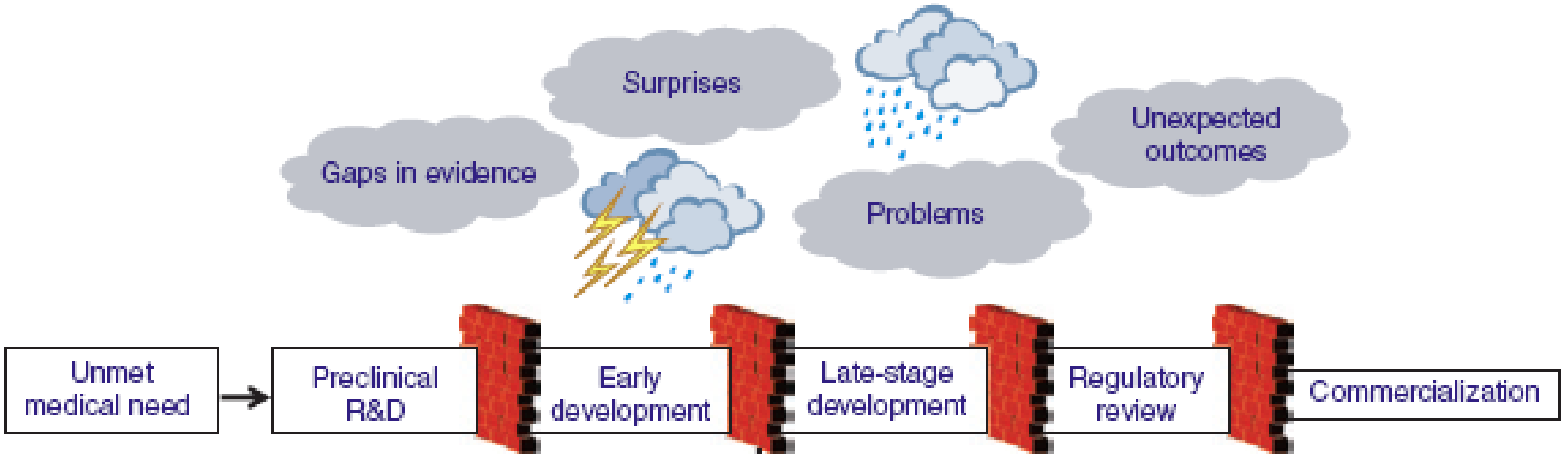


Using a quantitative pharmacology approach to support decision making, by establishing a translational *exposure –target engagement – efficacy/safety modelling in animals and humans and predicting the dose to man, optimal dosing schedule and clinical study design.*

Sandra Visser, Merck

The R&D process (time and decision involved)





Grasela and Slusser, Clin. Pharm & Ther, 2010, Vol 88:2 p263-268

New model based drug development approach (MBDD)

1. **Instead of discrete understanding (Yes and No) whether a drug efficacious and safe.**
2. **Increase confidence and understanding of Risk/benefit balance.**
3. **Allow relationship understand through model and estimation**
   - Quantitative assessment of effects and safety across dose range and population

MBDD integrates Dose-PK-PD (where PD may be response, desired and/or un-desired, effect on biomarkers etc) knowledge into models, aiming to increase understanding of the characteristics of a compound/group of compounds and to quantitatively evaluate study and program design and to predict probability of success.

Model Based Drug Development (MBDD) should play a fundamental role in projects decision-making across the value chain (from before first time in man to life cycle management).

MBDD – high impact examples (Pfizer)

6/9 involved model based dose-response analyses in phase IIb

Table 1 Some examples of the high-level efficiencies gained over historical designs and data analytics following MBDD implementation

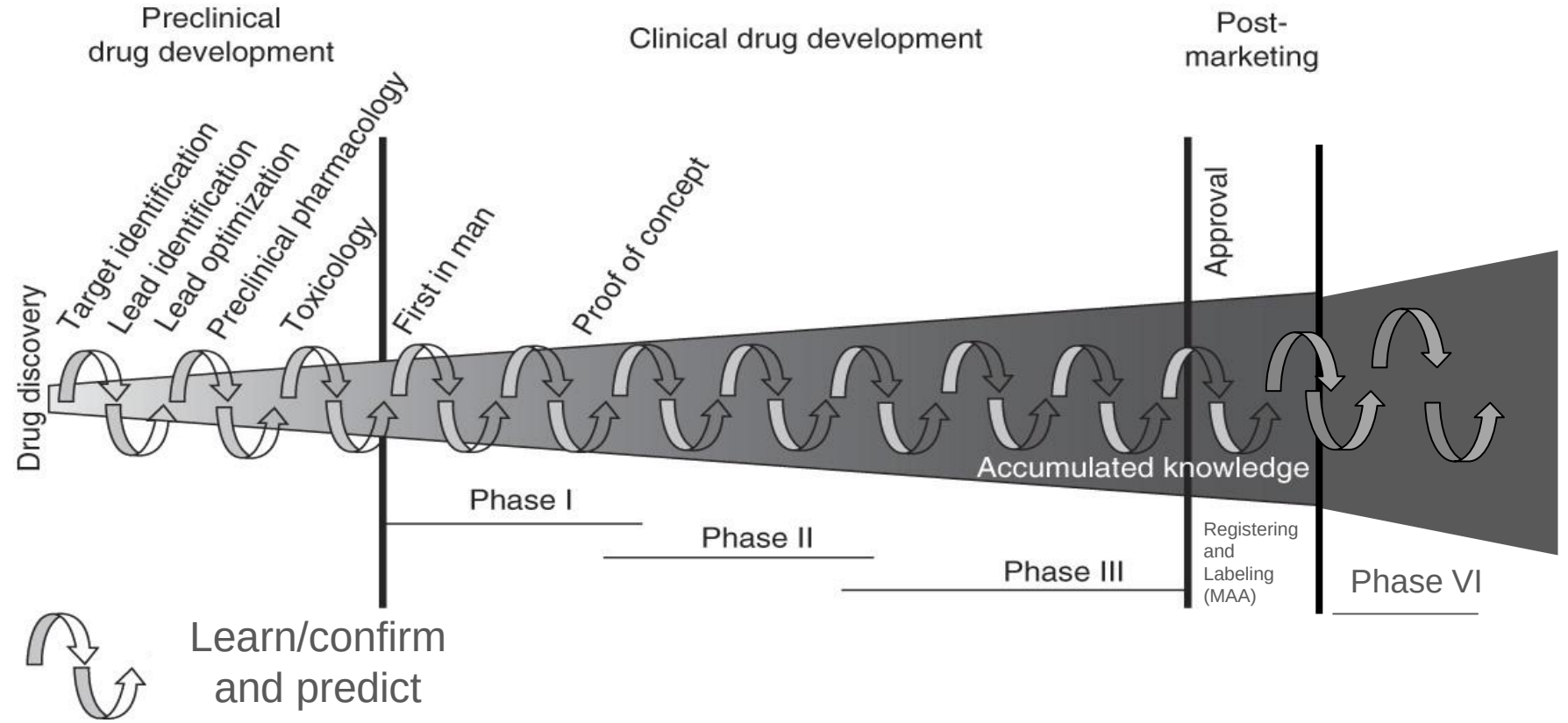
Indication	MBDD approach adopted	Efficiencies gained over historical designs and analysis
Thromboembolism[a]	Omit phase IIa, model-based dose–response relationship, adaptive phase IIb design	2,750 Fewer patients, 1 year shorter study duration
Hot flashes	Model-based dose–response relationship	1,000 Fewer patients
Fibromyalgia	Prior data supplementation, model-based dose–response relationship, sequential design	760 Fewer patients, 1 year shorter study duration
Type 2 diabetes	Prior data supplementation, model-based dose–response relationship	120 Fewer patients, 1 year shorter study duration
Gastroesophageal reflux	Model-based dose–response relationship	1,025 Fewer patients
Rheumatoid arthritis	Model-based dose–response relationship	437 Fewer patients, increased probability of success
Global anxiety disorder	Omit phase IIb	260 Fewer patients, 1 year shorter study duration
Lower urinary tract symptoms	Meta-analysis	Increased probability of success
Urinary incontinence	Meta-analysis	Increased probability of success

MBDD, model-based drug development.

[a]This application is discussed further in the text as example 4, "Adaptive dose-finding phase II study designed using clinical trial simulations."

Milligan, CPT 2013

Benefit/Risk decision and M&S continuum



Uncertainty

Confident and Drug and Disease

Paediatric Strategy & Investigation Plan — Early

Scientific Advice
Clinical Trial Application, Qualification of novel methodologies — Anytime

MAA + post lic. — Late

Adapted from Lalonde RL et al., Model-based drug development. Clin Pharmacol Ther 2007;82:21-32
And Shepard T, Role of Modelling and Simulation in Regulatory Decision Making in Europe, EMA-EFPIA M&S WS 2011

Modelling and simulation (M&S)

Hypothesis → drug development

Trials answer questions from hypotheses

Traditional approach → Data driven (more trials, higher cost)

M&S → integration → hypothesis → mathematical model (Validated with data)

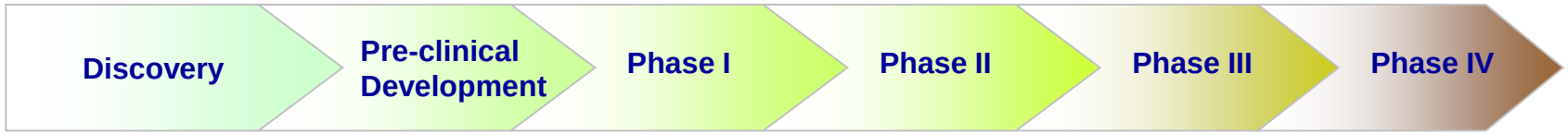
- **Numerical and *in silico* studies (H_0 → test (DDI) and refined (dose))**
- **Fewer trials, less cost**
- **'what if'→ study design + diff. H_0**
- **Info. (previous trials + literature)**

Accumulation of experience and knowledge of preparation for future studies design = efficient development path

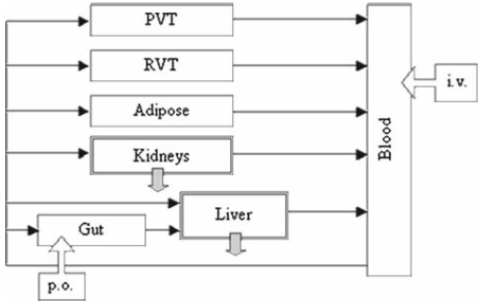
Avoid try and error approaches!

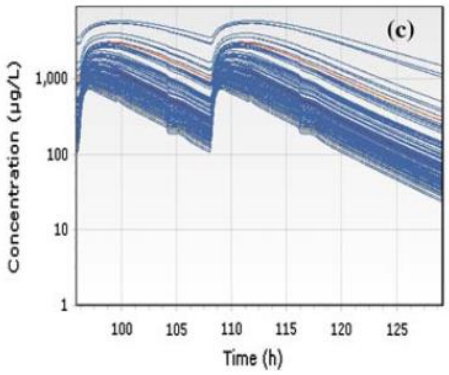
Examples

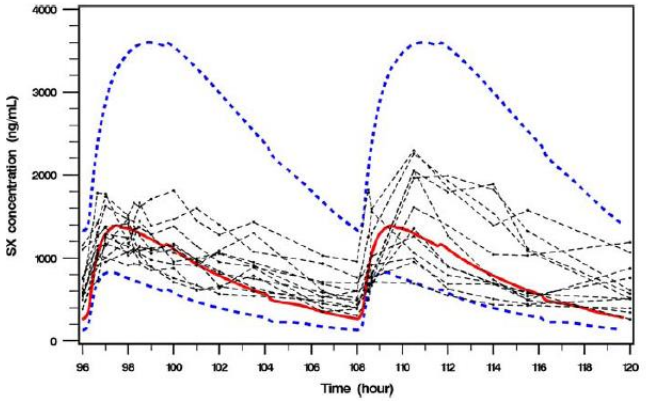
M&S in development process



PK Prediction and design of sampling scheme



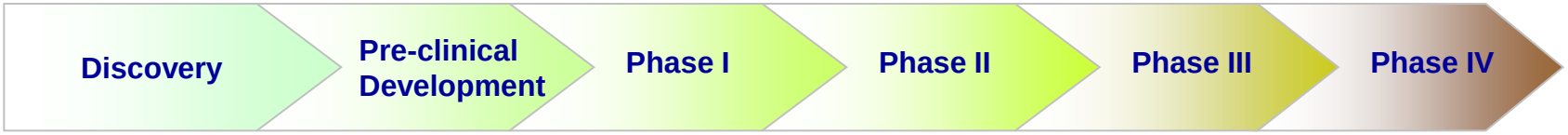




Develop PBPK model + variability → Fit model in NONMEM → Design trial using this pop model

Step 1 **Step 2** **Step 3**

M&S in development process



- **Primary:**
  - Safety
  - Tolerability
- **Secondary:**
  - Pharmacokinetics (PK)
  - Anti-tumour activity (Early Efficacy Signal)
- **Exploratory**
  - Pharmacodynamics (PD) and PoM Biomarkers

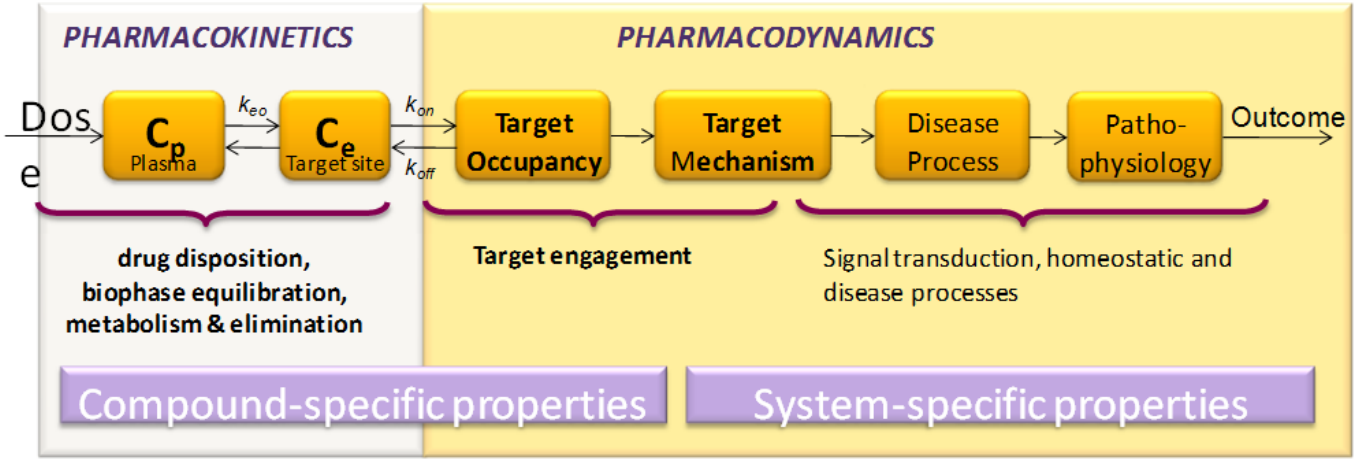
Translational and Dose escalation: PhI Oncology SAD and MAD

- **Oncology: Compounds generally unsuitable for healthy volunteers and studies often enrol patients for whom all other standard therapies have failed**
- **Sets recommended dose and schedule for rest of program e.g. Phase II/III**
- **Understand PK-PD-Safety-Efficacy relationship for future trials**
- **A range of administration schedules may also be studied e.g. intermittent vs. continuous**
- **Study design aim: To escalate the dose in steps to identify Maximum Tolerated Dose (MTD) and a Recommended Dose (RD) for future studies which balances safety and efficacy (PD effect) and vs. maximising the number of patients that receive a therapeutic dose.**
- **Multiple dose escalation methods available**

Could a population model based approach be more suitable?

Data integration and variability assessment

- The rule based approach lacks of understanding of all the data available.
- The common model based approach lacks exposure-response at a population level.
- Integration:



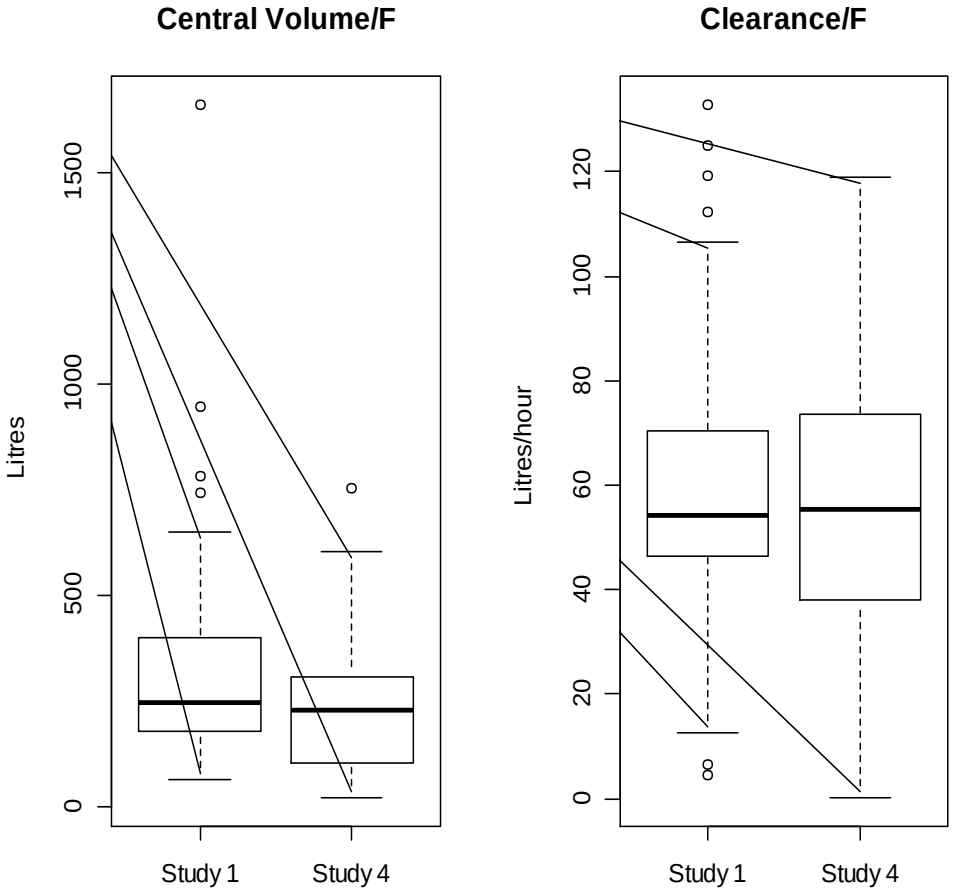
Sandra Visser

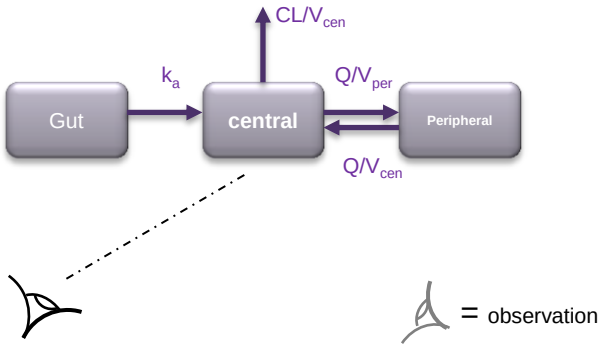
Emerging paradigm for efficacy – why not safety?

Hence the incorporation of:

- Preclinical modelling result/ information– enables model continuum
- Emerging trial data
- Population model based approach – allow understanding of underlying mechanism and relationship between exposure, target engagement and safety during escalation

Population PK analysis demonstrates similar pharmacokinetics in Western and Japanese patients





Confidence in similar dose escalation and scheduling approach

Study 1 = Western
Study 4 = Japanese

Simulating missed dose management strategy

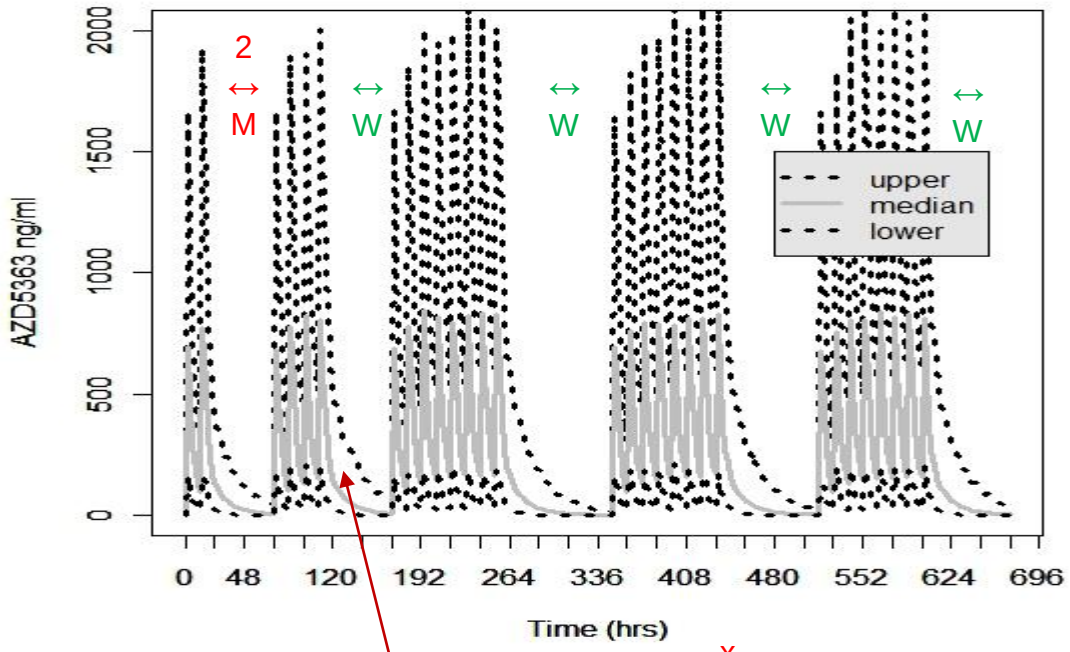
Early Population PK is used to guide trial design

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	1	2	3	4	5	6	7
Example	√	X	X	√	√	!	!	√	√	√	√	!	!	!	√	√	√	√	!	!	!	√	√	√	√	!	!	!

Questions:

- Can you resume and complete 4 days of dosing after an interruption due to toxicity?
- Should you stop and start at the next cycle?

Intermitted BID simulation scenario



Based upon on the simulated upper exposure range:

- If only 1 day of dosing is missed, then it is acceptable to complete the 8 doses with a reduced washout period.
- If two days are missed then one can administer 6 doses on that cycle.

If more days are missed, then restart at the next cycle.

Completing 6 doses after interrupting 1st cycle, still provides adequate washout before 2nd cycle

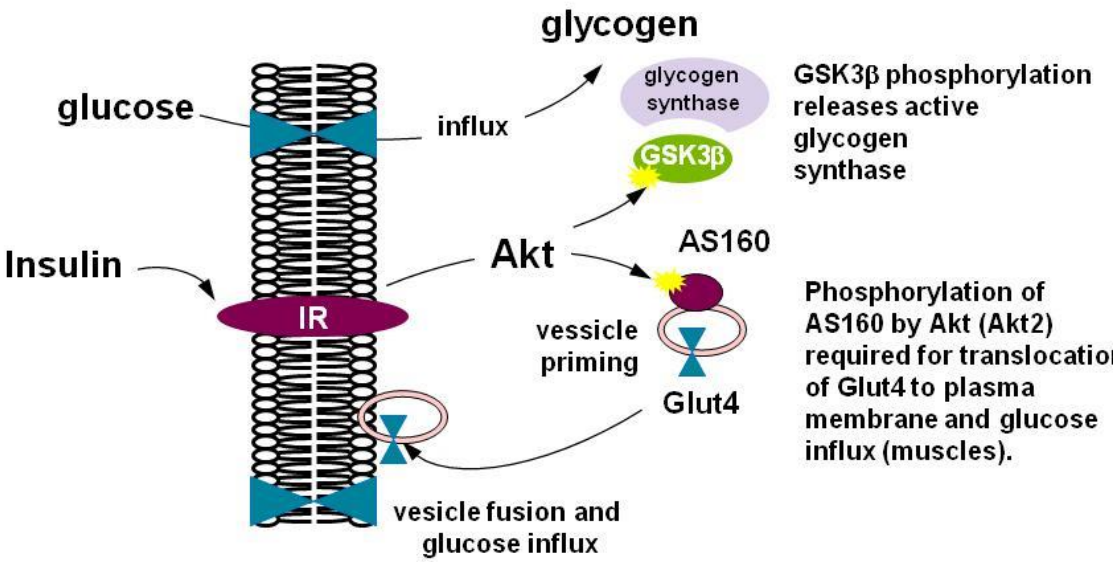
x
↔
M = x day missing doses

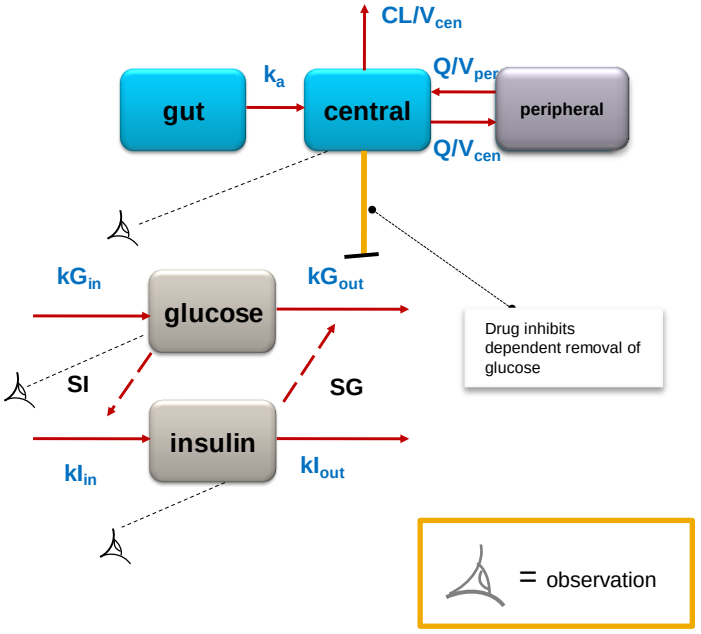
↔
W = washout period

AKT component of insulin dependent glucose uptake

Model developed using pre-clinical data

Akt required for translocation of glucose transporters from cytoplasmic to fuctional plasma membrane location, in response to insulin receptor activation. Akt phosphorylation of GSK3β relieves inhibition of glycogen synthase and co-ordinates glucose influx and glycogen storage.



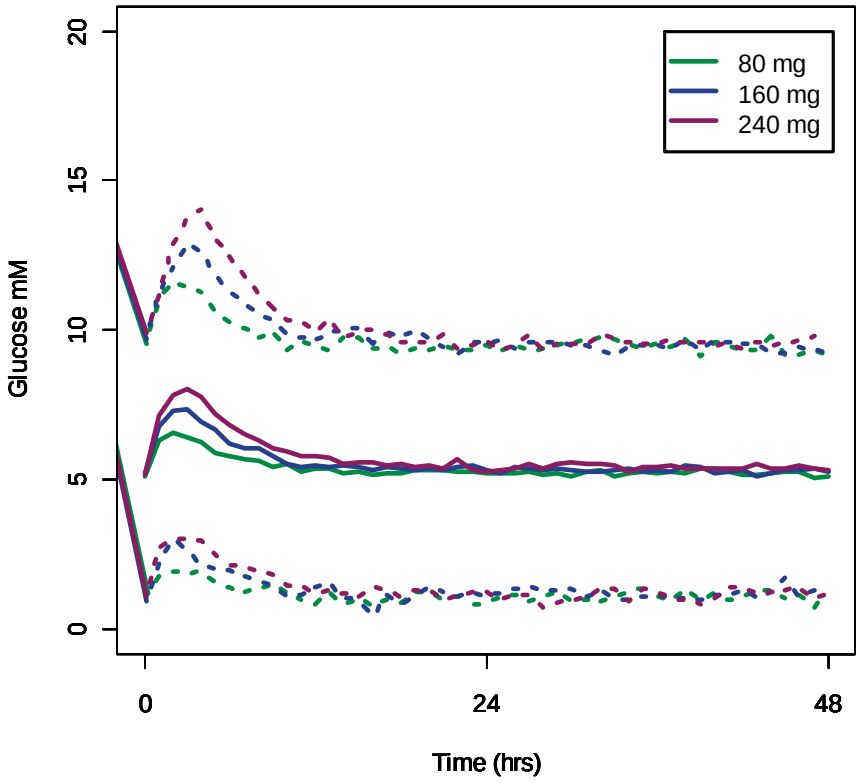


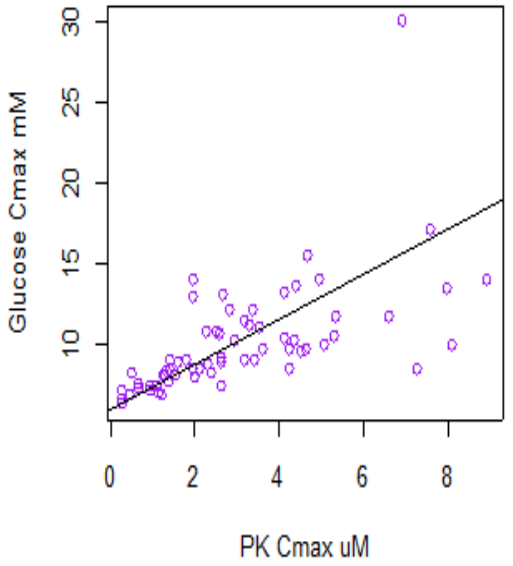
Akt inhibition by AZD5363 results in increased plasma glucose (inhibition of Glut4 function) and increased plasma insulin (dynamic response to elevated plasma glucose).

Population modelling guides dose escalation

PK- glucose relationship extrapolated to higher doses

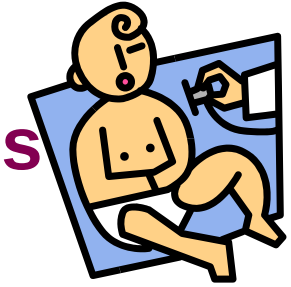
Simulation of medium effects (97.5% upper quantile shown below)



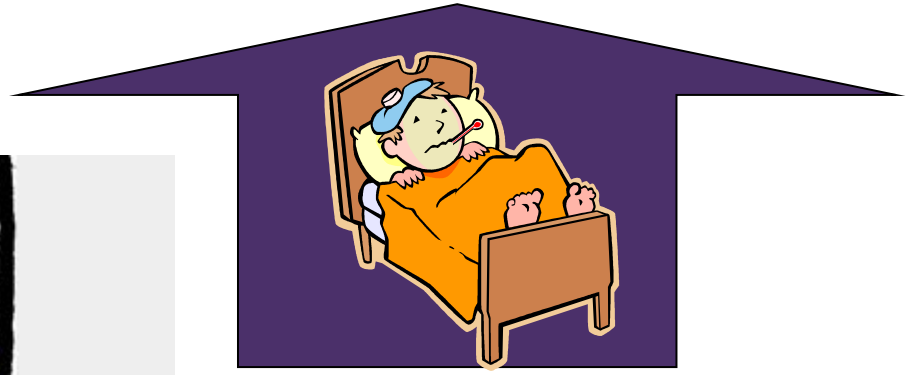


Blood sugar back to baseline during 'off drug' days

M&S in development process



Discovery → Pre-clinical Development → Phase I → Phase II → Phase III → Phase IV



Paediatric

http://www.medicalobserver.com.au/news/medicines-need-to-meet-the-toddler-taste-test

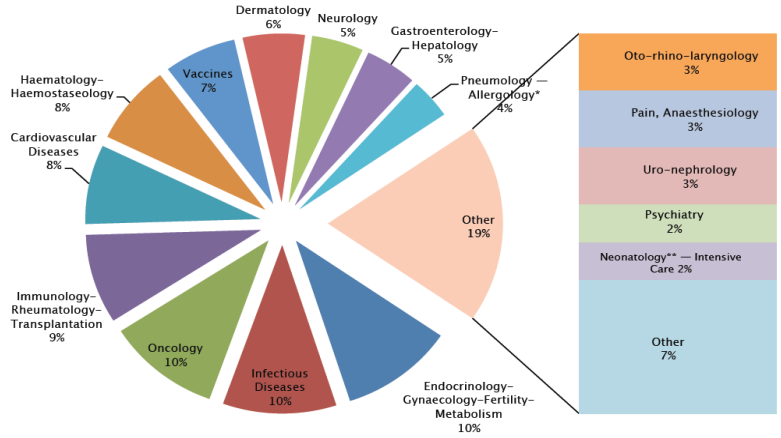
Paediatric medicine status

It is important to improve current medicine for children because it is an area of unmet need.

The key objectives of the Regulation are:

- to ensure high-quality research into the development of medicines for children;
- to ensure, over time, that the majority of medicines used by children are specifically authorised for such use with appropriate forms and formulations;
- to ensure the availability of high-quality information about medicines used by children.

Therapeutic areas addressed by the paediatric investigation plans (2007-2011)

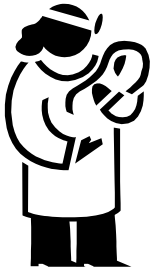


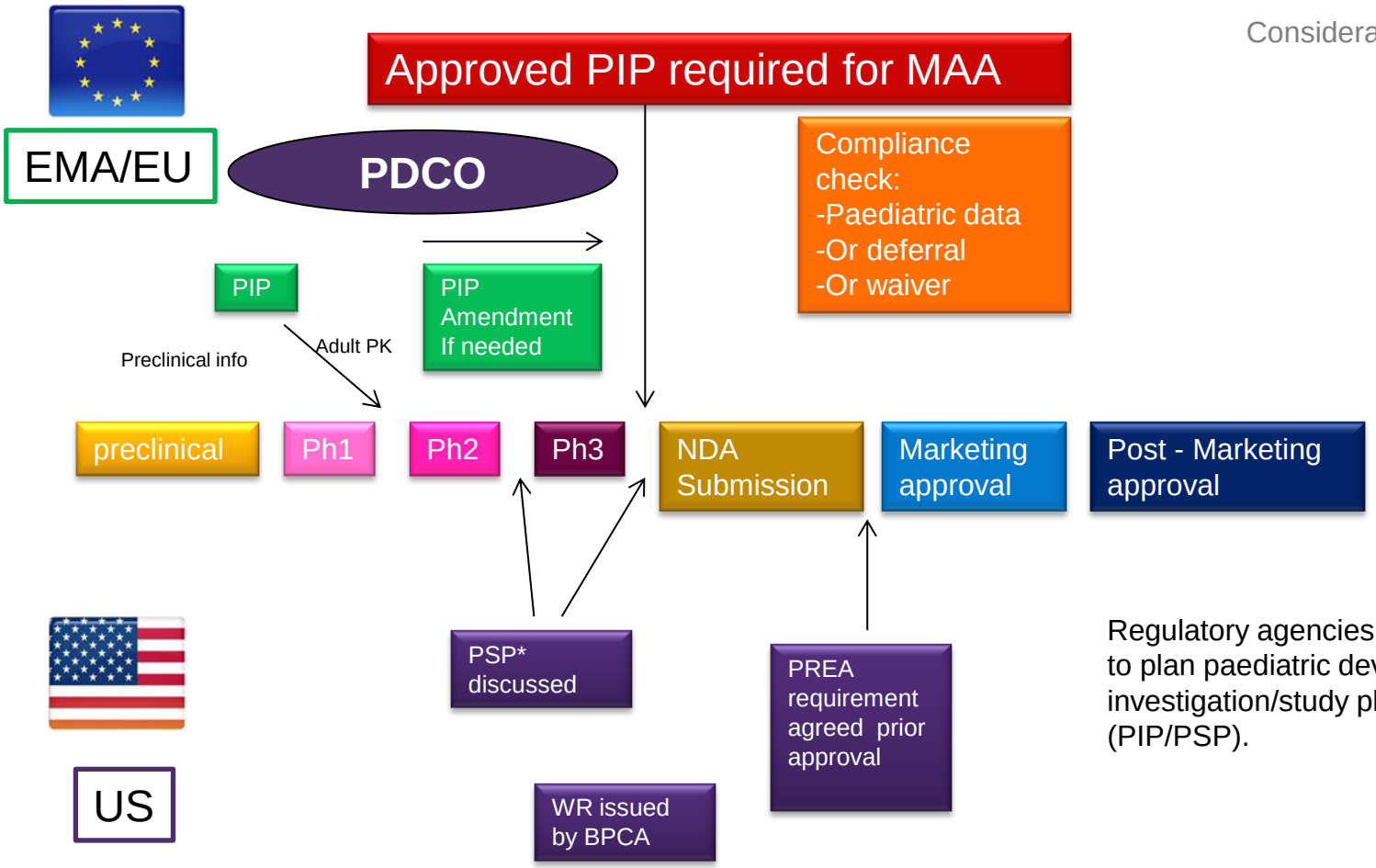
Source: EMA Paediatric database.
* Excluding allergen products.
** Applications that exclusively address a use in neonates.

Number of children to be enrolled in clinical trials

Number of subjects	2006	2007	2008	2009	2010	2011	2012
Preterm newborns	0	0	0	207	82	2 281	1 712
Newborns	0	0	5	64	169	1 105	1 172
Infants and toddlers	330	21	20	59	351	2 788	3 141
Children	2 142	181	200	2 230	2 055	10 325	20 677
Adolescents	368	111	205	1 577	2 861	9 054	13 193
Sum of above	2 840	313	430	4 137	5 517	25 553	39 895
Reference: number of paediatric trials	316	355	342	404	379	334	332

Source: EudraCT Data Warehouse using a pre-defined query on 6 March 2013, modified by excluding studies for 'immunological medicinal products'





Consideration also required for:
Japan
China
Australia
Canada etc

Regulatory agencies have requirements to plan paediatric development: paediatric investigation/study plan in Europe/US (PIP/PSP).

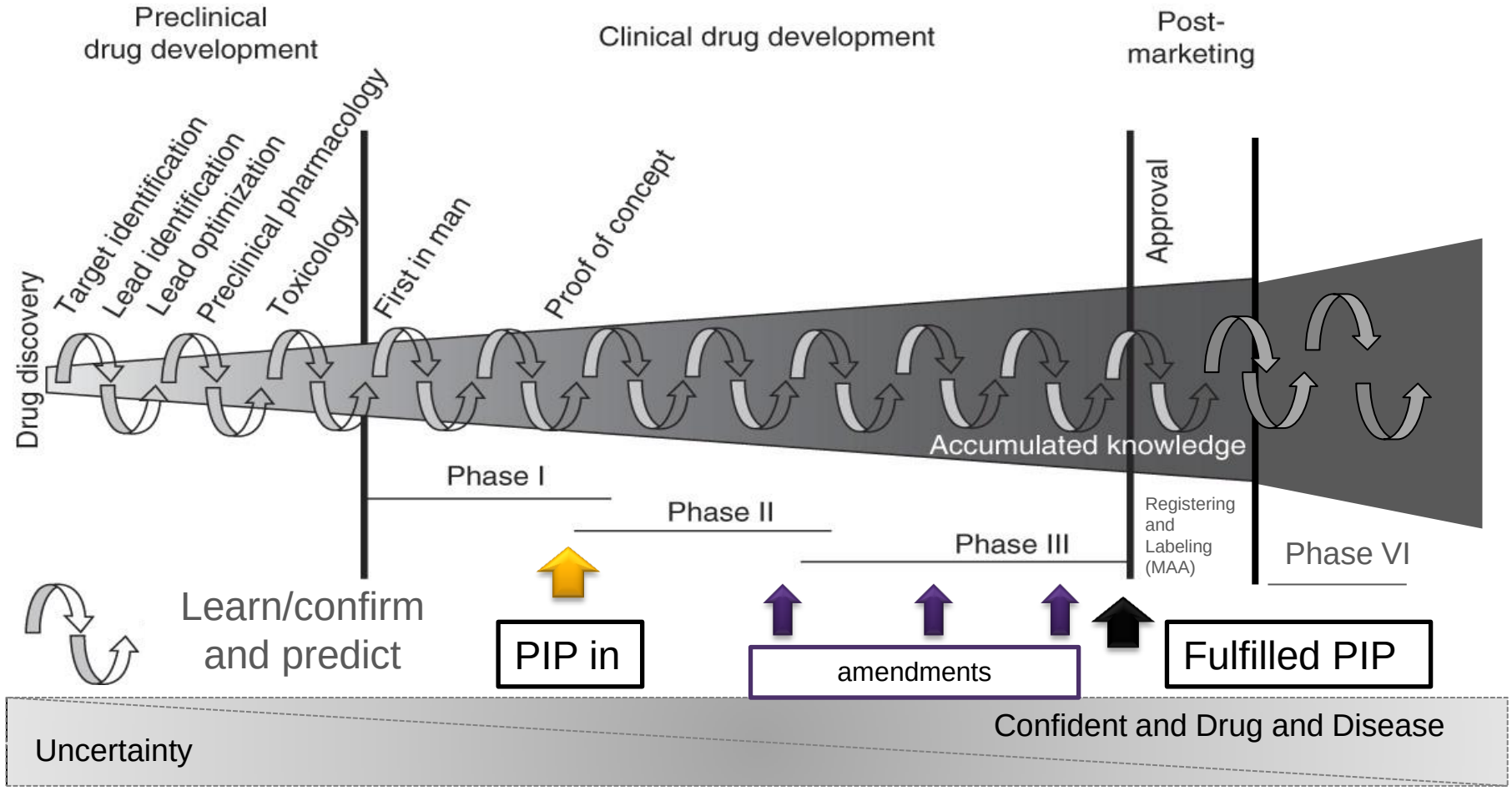
*currently new guidance are being updated

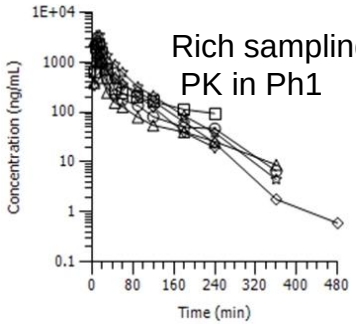
Clinical paediatric trial consideration?

- What do we want the trial to tell us?
- What do we need to assume?
- Age appropriate Formulation
- Feasibility on location of sampling?
- Blood volume limitation (ICH-11, WHO, many guidance existed)
- SAD and MAD?
- Rich sample sparse sampling?
- Can single dose predict steady state?
- Consideration of micro-sampling: Wet and dry (Dry Blood Spot)?
- Drug-Drug Interaction (DDI)?
- PD?

Conclusion: Many consideration and it's not simple

Benefit/Risk decision and M&S continuum





Rich sampling PK in Ph1

Paediatric Strategy & Investigation Plan

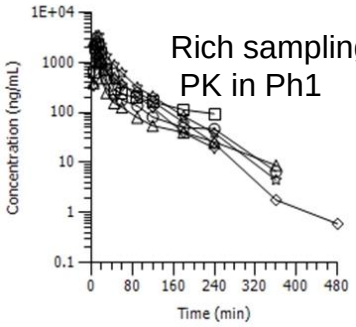
Early

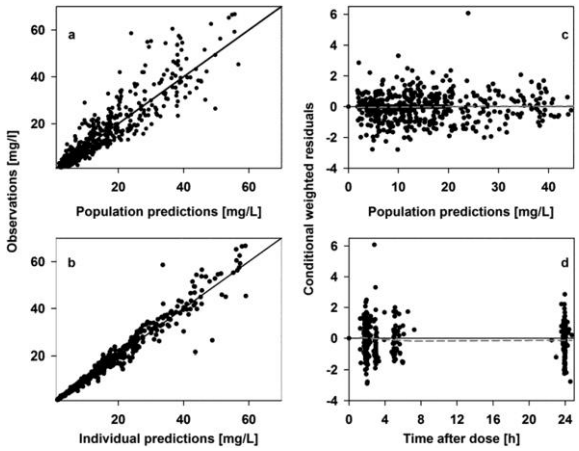
- Adult dose-exposure (PK)-response (PD) ,DER, relationship
- DER similar in adult and paediatric population
- Age groups differences in exposure
- Biomarker/safety response similar?

Limited data collected in trial potentially (issues in both adult and children trials) : Population PKPD approach

Non-linear Mixed effect modelling (across species)

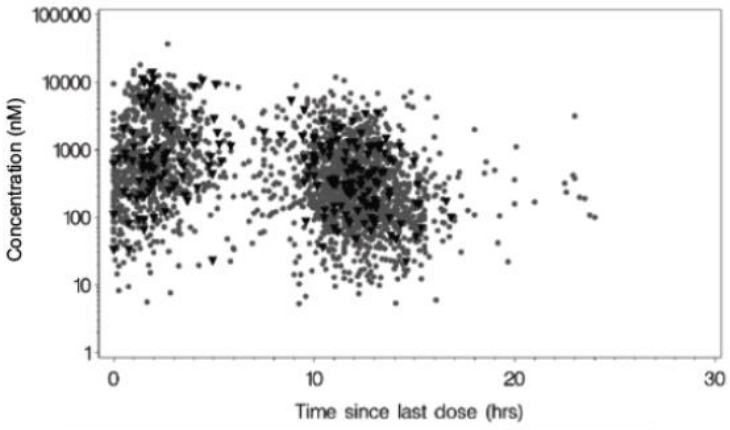
- **Utilise all data (rich sampling and sparse) in a population levels**
- **Understand inter and intra individual variability**
- **Covariate effect (on ADME)**
- **Incorporation of Bayesian methodology (prior distribution)**
- **Regulatory acceptance**





Population modelling diagnostic plot

Sparse sampling PK in Ph2



Cheung SYA AP, AZ 28 Jan 2014

Plots are for illustration purposes

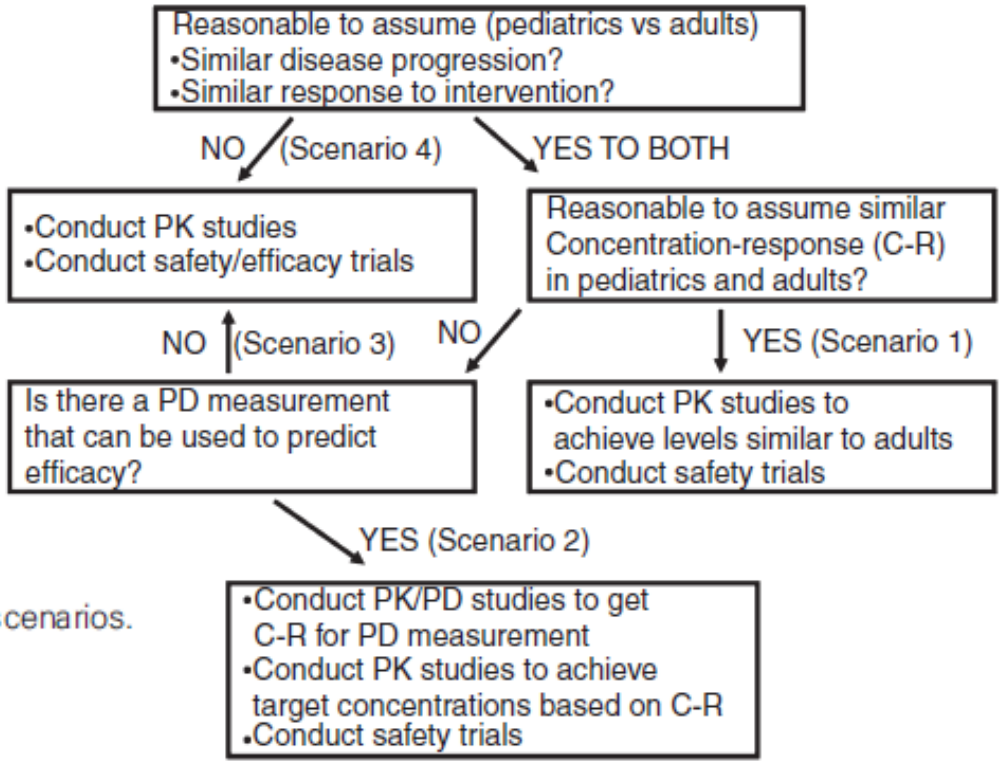
Role of modeling and simulation in pediatric investigation plans

Efthymios Manolis, Tariq Eldirdiry Osman, Ralf Herold, Franz Koenig, Paolo Tomasi, Spiros Vamvakas & Agnes Saint Raymond

European Medicines Agency, Canary Wharf, London, UK

Similar idea for FDA:

Guidance for Industry: Exposure-Response Relationships



Pediatric study decision tree with identified scenarios.

Each scenario requires a thorough understanding of the pathophysiology of the disease, the developmental differences between adults and children that could have an impact on PK, PD, safety, and efficacy and of the mechanism of action of the drug. Any doubt will make extrapolation of the efficacy questionable.

Scenario 1: Extrapolation of efficacy is possible between adults and children based on achieving similar PK between the two populations. In practice, we assume similar therapeutic effect with the same PK exposure.

Scenario 2: Extrapolation of efficacy is possible between adults and children based on achieving similar PD between the two populations. In practice, we assume similar therapeutic effect with the same PD value.

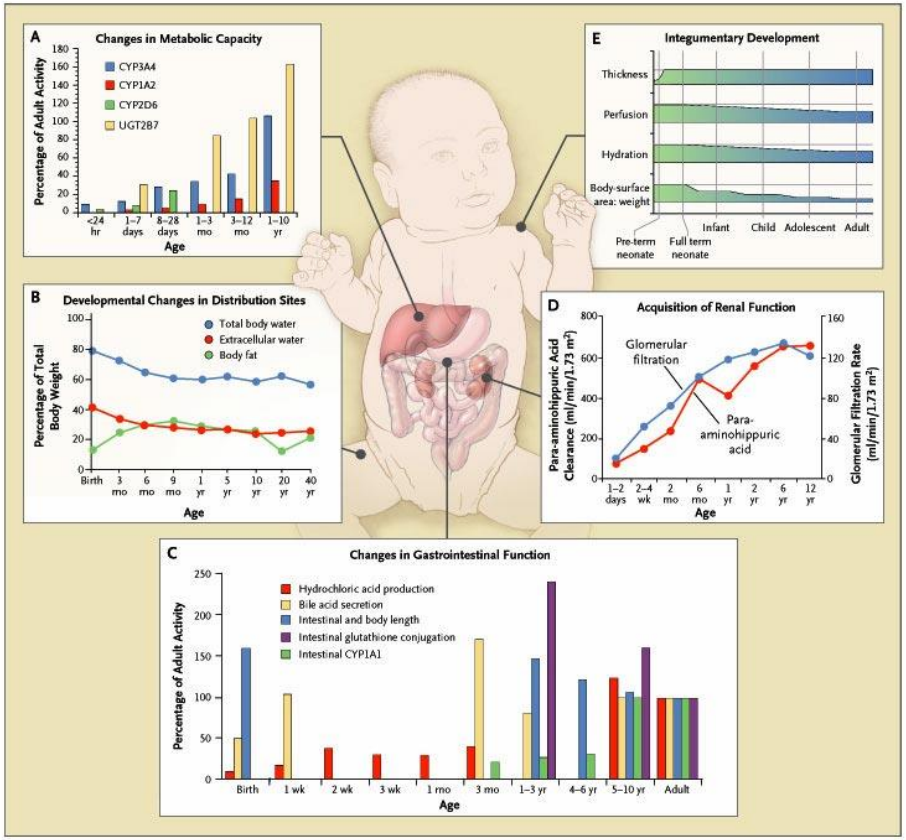
Scenario 3: Extrapolation of efficacy is not possible between adults and children even if disease progression and response to intervention can be considered similar. The reason for this is that there is not a PK or PD measurement that can be used as a surrogate for efficacy.

Scenario 4: Extrapolation of efficacy is not possible because the disease and response is not considered similar between adults and children.

The scenarios are described for extrapolation between adults and children but can be also applicable for extrapolation between different pediatric age groups.

Children are not small adult!

Growth, maturation/ontogeny



Kearns, G. L. et al. N Engl J Med 2003;349:1157-1167

Draft guidance Paediatric PK study 1998

Group	Age
Neonate	< 1 month
Infant	1 month – 2 years
Child	2-12 years
Adolescent	12-16 years
'Mini Adult'	16-<18 years

•Continuous development from embryo to adolescent
Body composition (weight, height)
Organ function (e.g. lung, liver, kidney)
ADME changes (ontogeny /maturation)

- A: Gastric acid &GI emptying &feasible route of admin
- D: Volume distribution, diff fat & body water & transporter, protein
- M: Drug metabolizing enzymes (CYPs)
  - Unique metabolic pathways
- E: renal

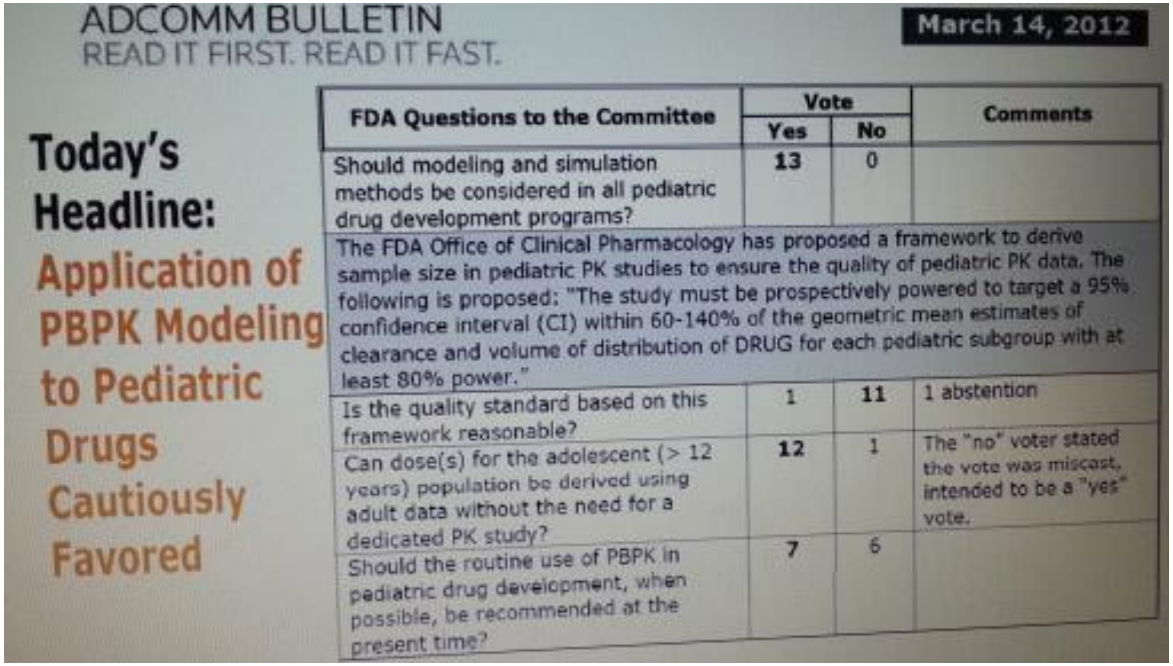
Receptor response (pathway, safety) Data?
Appearance Clearance: important parameter

Dose = CL/F * AUCtau

But to what extend we will use 0.75 as a factor of allometric scaling?

Outline: PBPK modelling

What is PBPK modelling approach?
Why we are using it?
Regulatory view
Both Europe and US
Examples



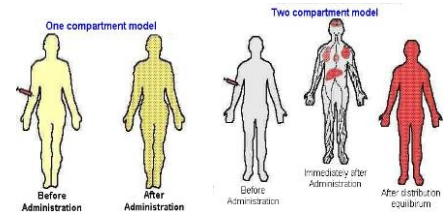
ADCOMM BULLETIN
READ IT FIRST. READ IT FAST.

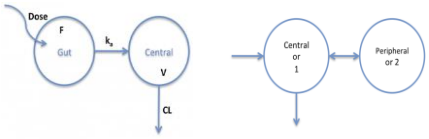
March 14, 2012

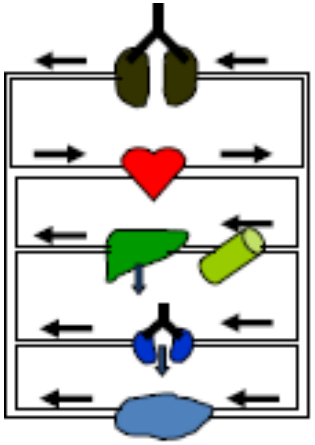
Today's Headline:
Application of PBPK Modeling to Pediatric Drugs Cautiously Favored

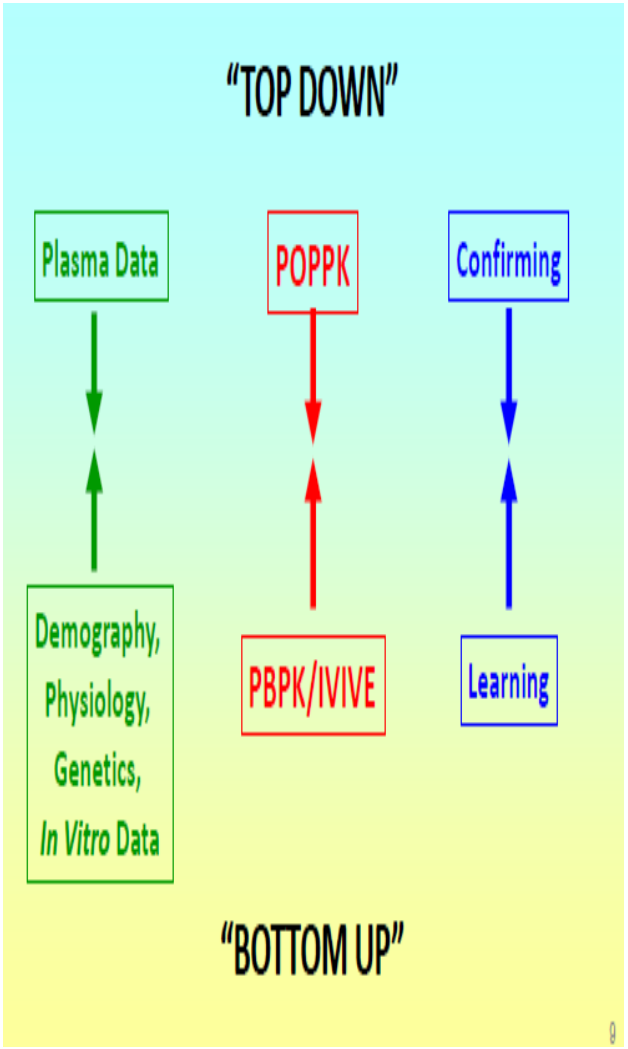
FDA Questions to the Committee	Vote		Comments
	Yes	No	
Should modeling and simulation methods be considered in all pediatric drug development programs?	13	0	
The FDA Office of Clinical Pharmacology has proposed a framework to derive sample size in pediatric PK studies to ensure the quality of pediatric PK data. The following is proposed: "The study must be prospectively powered to target a 95% confidence interval (CI) within 60-140% of the geometric mean estimates of clearance and volume of distribution of DRUG for each pediatric subgroup with at least 80% power."			
Is the quality standard based on this framework reasonable?	1	11	1 abstention
Can dose(s) for the adolescent (> 12 years) population be derived using adult data without the need for a dedicated PK study?	12	1	The "no" voter stated the vote was miscast, intended to be a "yes" vote.
Should the routine use of PBPK in pediatric drug development, when possible, be recommended at the present time?	7	6	

Empirical Approach vs. Mechanistic Approach

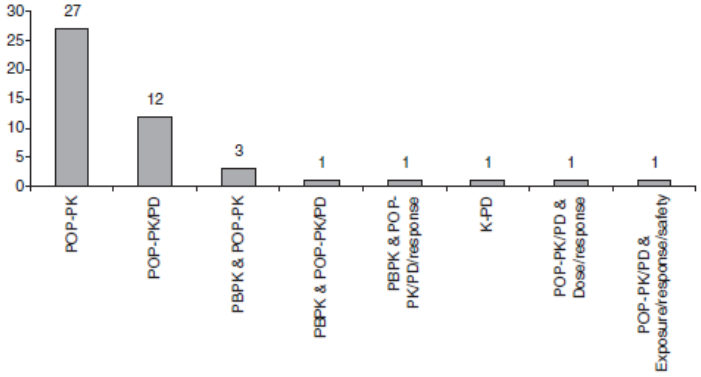








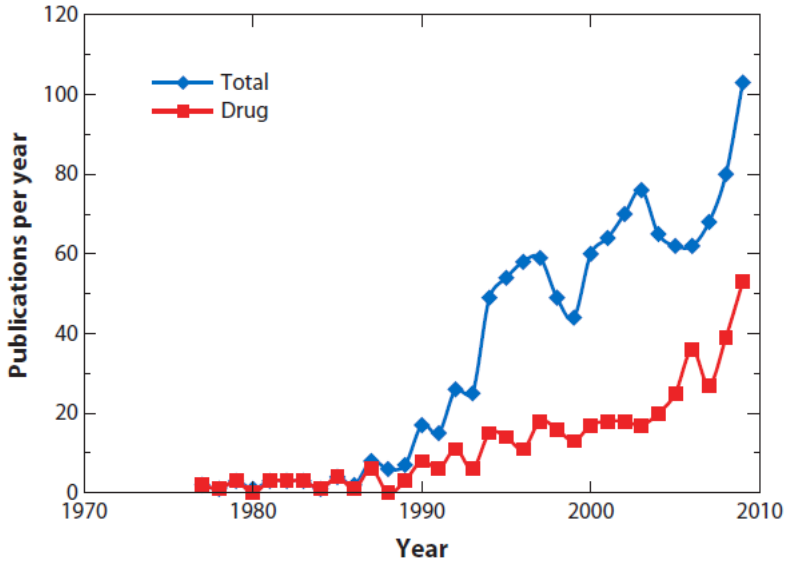
Consideration:
- Objective
- Assumption
- Amount and quality of data
- Extrapolation? Extend?

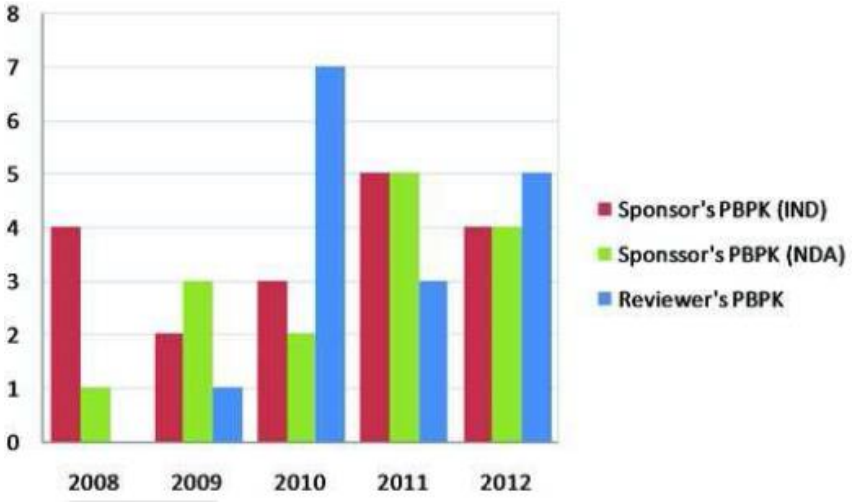


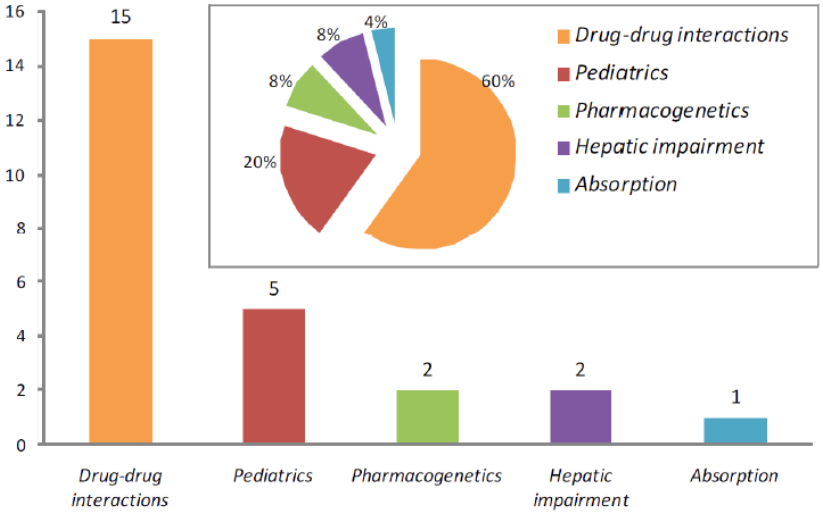
M&S in positive PIP opinion (as of Jan 2010). Model types and number of opinions with reference to specific model types.

Manolis et al. Ped Anes 21: 214-221 (2011)
Simcyp 2013

Application of physiologically based PK/PD model (PBPK/PD)







From July 2008 to June 2012, the FDA reviewed 18 IND and 15 NDA submission containing PBPK M&S to support clinical pharmacology by sponsors. In addition, FDA reviewers conducted PBPK M&S to support review of another 16 submission which sponsor did not use PBPK

Distribution of clinical pharmacology question addressed by PBPK among submission over the period of Jun 2008 and Dec 2011

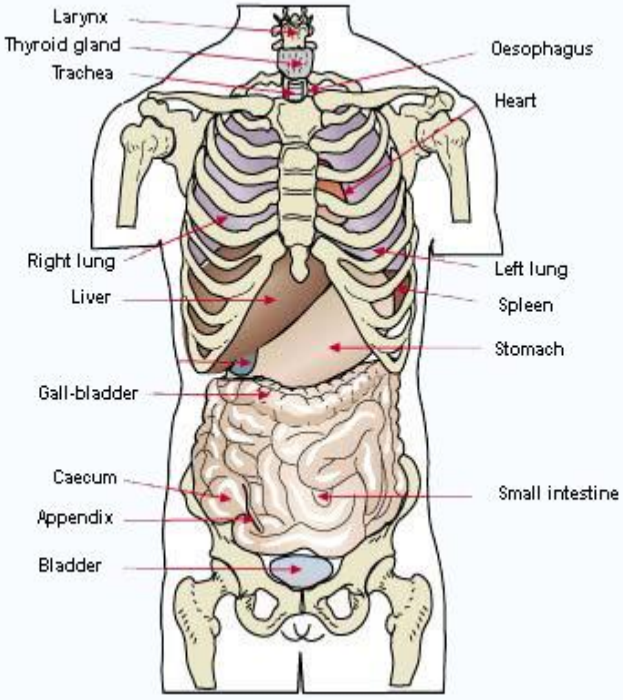
Rowland, Peck, Tucker 2011 Annu. Rev. Pharmacol. Toxicol.
Zhao et al, 2011 Clin. Pharm. Ther
Zhao et al, 2012 Clin Pharm Ther
Huang et al, 2013 J Pharm Sci

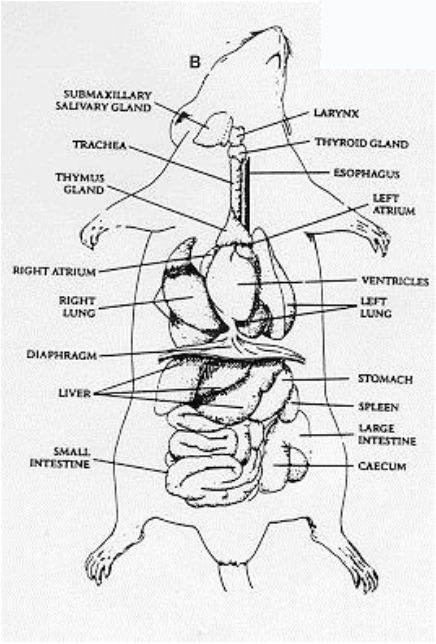
Background

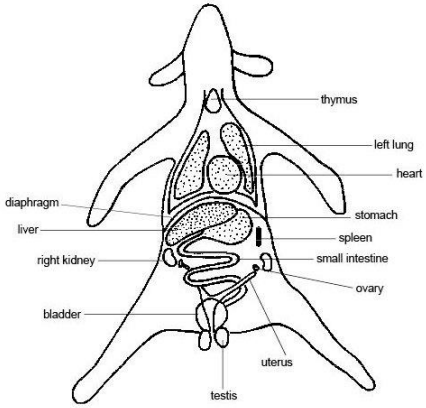
- **Mammalian body consist of a number organs/tissues that are interconnected**

- **Organs between species**
- Common link via blood circulation through heart, lung and blood v
- Vital organs are similar in function such as brain, heart , lung
- Sizes and ADME process are different
- Similarity allow us to understand cross-species PKPD in species , drug development

- **In humans, organs form systems:**
- 11 major systems
  - Cardiovascular
  - Respiratory
  - Digestive
  - Endocrine
  - Excretory
  - Reproductive
  - Skeletal
  - Integumentary
  - Muscular
  - Nervous
  - Immune system

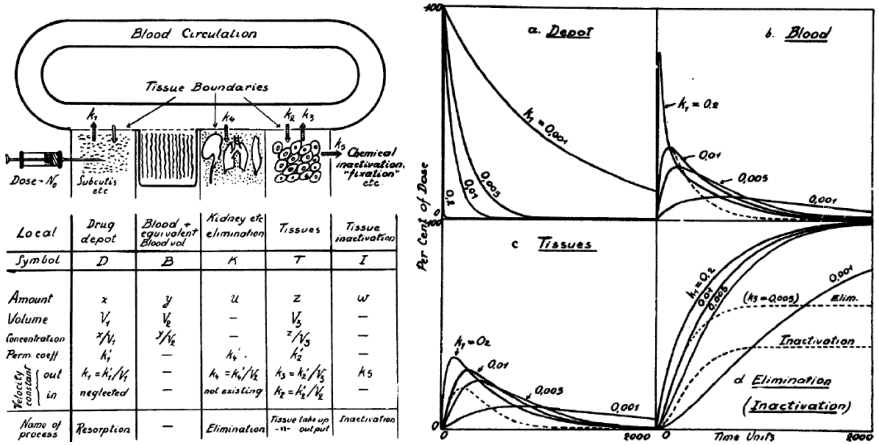






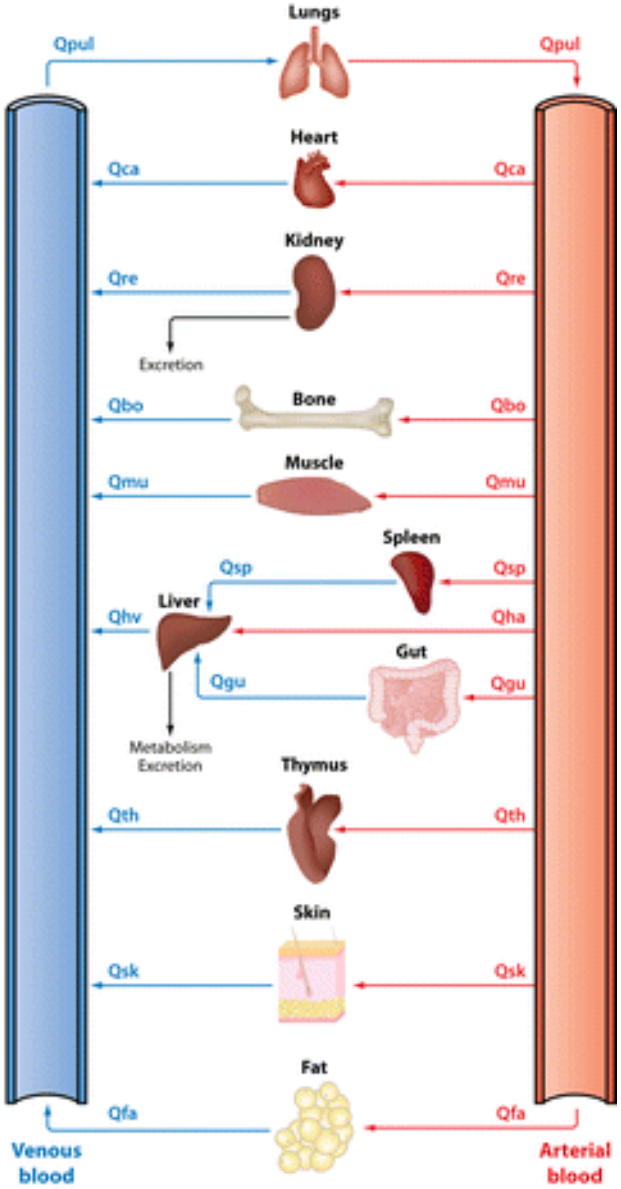
PBPK: Physiologically Based Pharmacokinetic model

- **It's not a new science but evolving**
- **First discussed by Teorell T. 1937**



Local	Drug depot	Blood + equivalent Blood vol	Kidney etc elimination	Tissues	Tissue inactivation
Symbol	D	B	K	T	I
Amount	x	y	u	z	w
Volume	V_1	V_2	–	V_3	–
Concentration	x/V_1	y/V_2	–	z/V_3	–
Perm coeff	k_1'	–	k_4'	k_2'	–
Velocity constant out	$k_1 = k_1'/V_1$	–	$k_4 = k_4'/V_2$	$k_3 = k_2'/V_3$	k_5
Velocity constant in	neglected	–	not existing	$k_2 = k_2'/V_2$	–
Name of process	Resorption	–	Elimination	Tissue take up -in- out put	Inactivation

- Not restricted to mammal, as in environmental tox. and risk
- Aim: PBPK model reflects the physiological structure that we have knowledge on such as blood flow rate and tissue volume to understand underlying mechanism

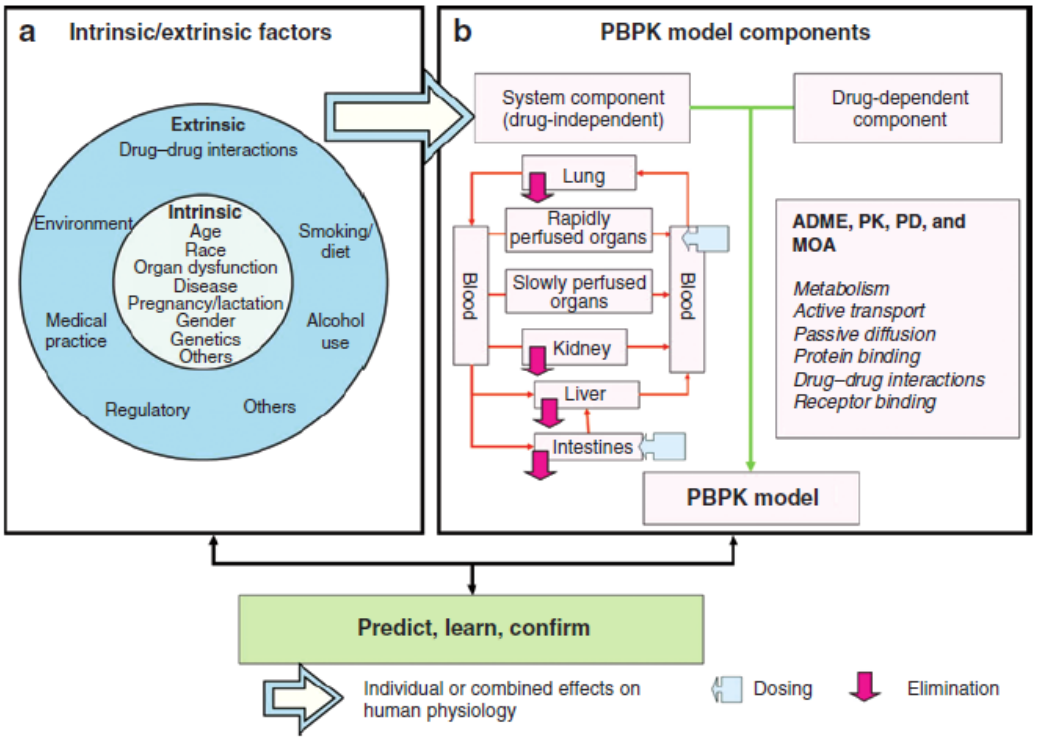


Rowland M, et al. 2011.
Annu. Rev. Pharmacol. Toxicol. 51:45–73

The Physiological (PBPK) Approach

•Incorporates known physiological parameters and overlays compound specific properties into a single model structure
•Estimate kinetics in a target tissue or organ (effect compartment)
• Evaluate the effect of various intrinsic (age, race, gender, disease, etc.) and extrinsic (DDI, environment, smoking, etc.) factors on drug exposure and response
•Model variability & uncertainty

User friendly software imbedded or allow software development e.g.:
• Simcyp, PK-Sim & SimulationPlus, Gastro-plus
• NONMEM, MATLAB, ACSLX

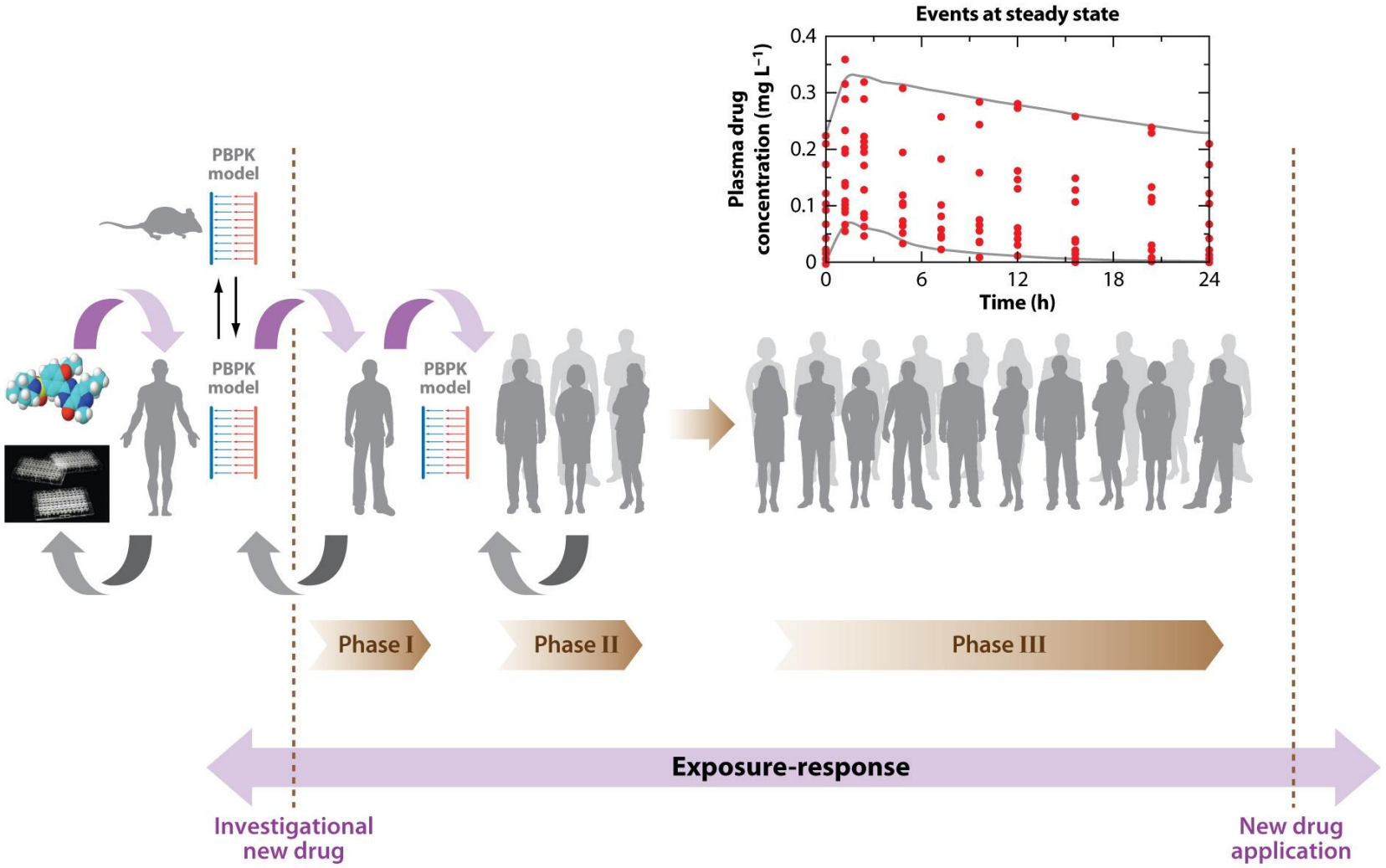


The degree of complexity of the PBPK model can vary according to the need.

Zhao et al, 2011 Clin. Pharm. Ther

Usage of PBPK model:

- A prior prediction of PK
- Understanding of the impact of changes in metabolism and transporter on PK and toxicity effects
- Effective and integrative use of in-vitro and in-vivo data
- Accumulating knowledge of the estimated kinetics (effect) compartments that will be useful for same compound class
- Extrapolation across species, routes of administration and doses
- Special populations such as paediatric, obese and elderly



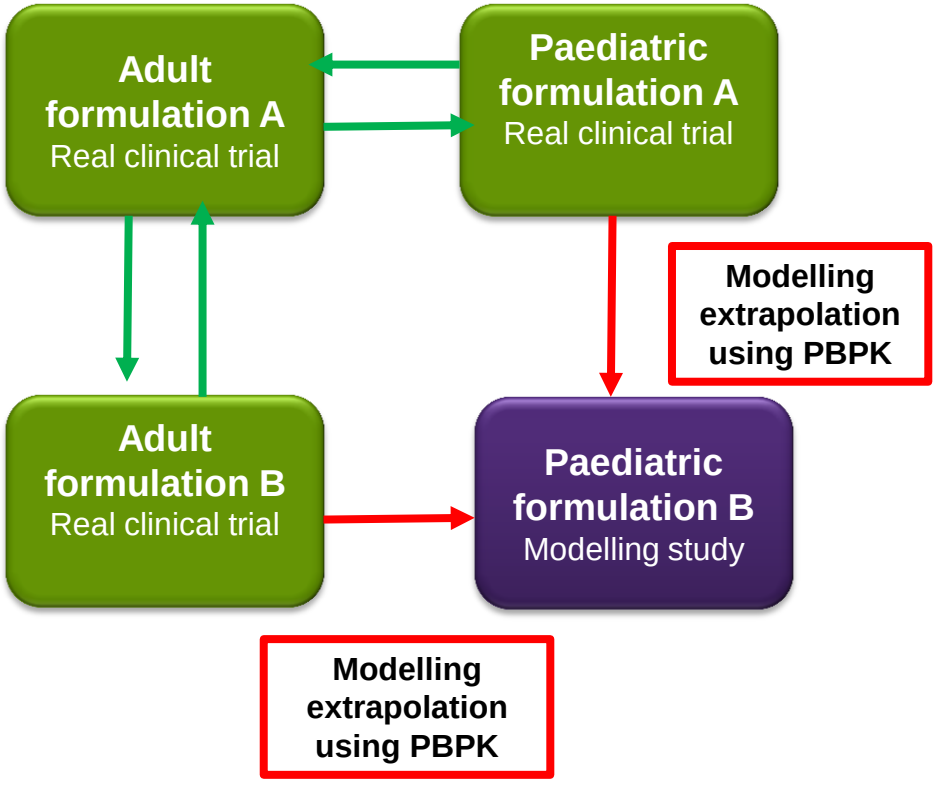
Rowland M, et al. 2011.
Annu. Rev. Pharmacol. Toxicol. 51:45–73

Formulation extrapolation

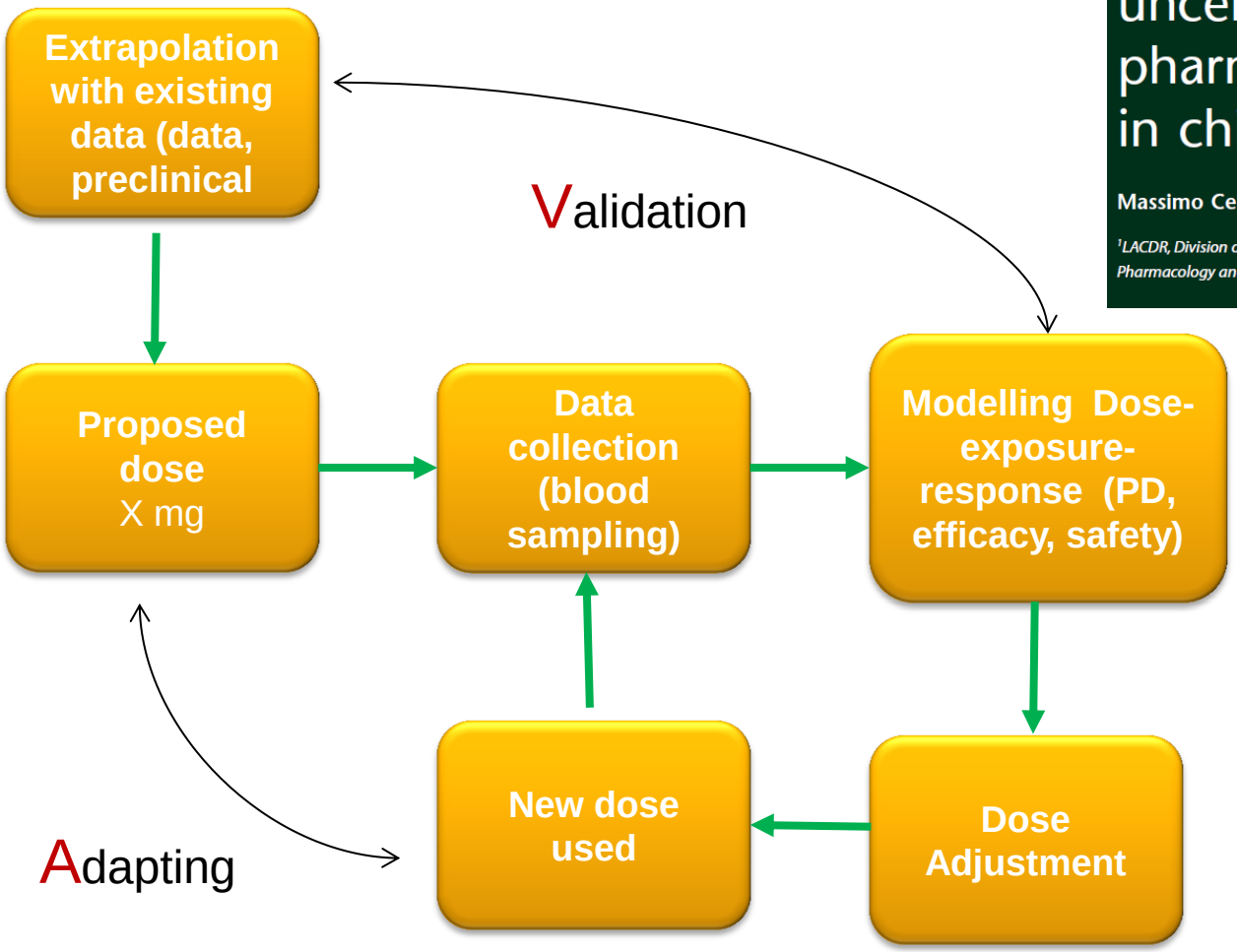
Assumptions:
- Similar disease/progression
- Similar response to treatment

Validate in adult in two formulation in PBPK model
Adult & Paed. PBPK Comparing PK parameters:
- Absorption, CL/f, V
- AUC/Cmax

Allow investigation of DDI aspects, CYPs, transporter and UGT
Ethical to avoid unnecessary trial & increase for other paediatric development



Adaptive protocol and modelling

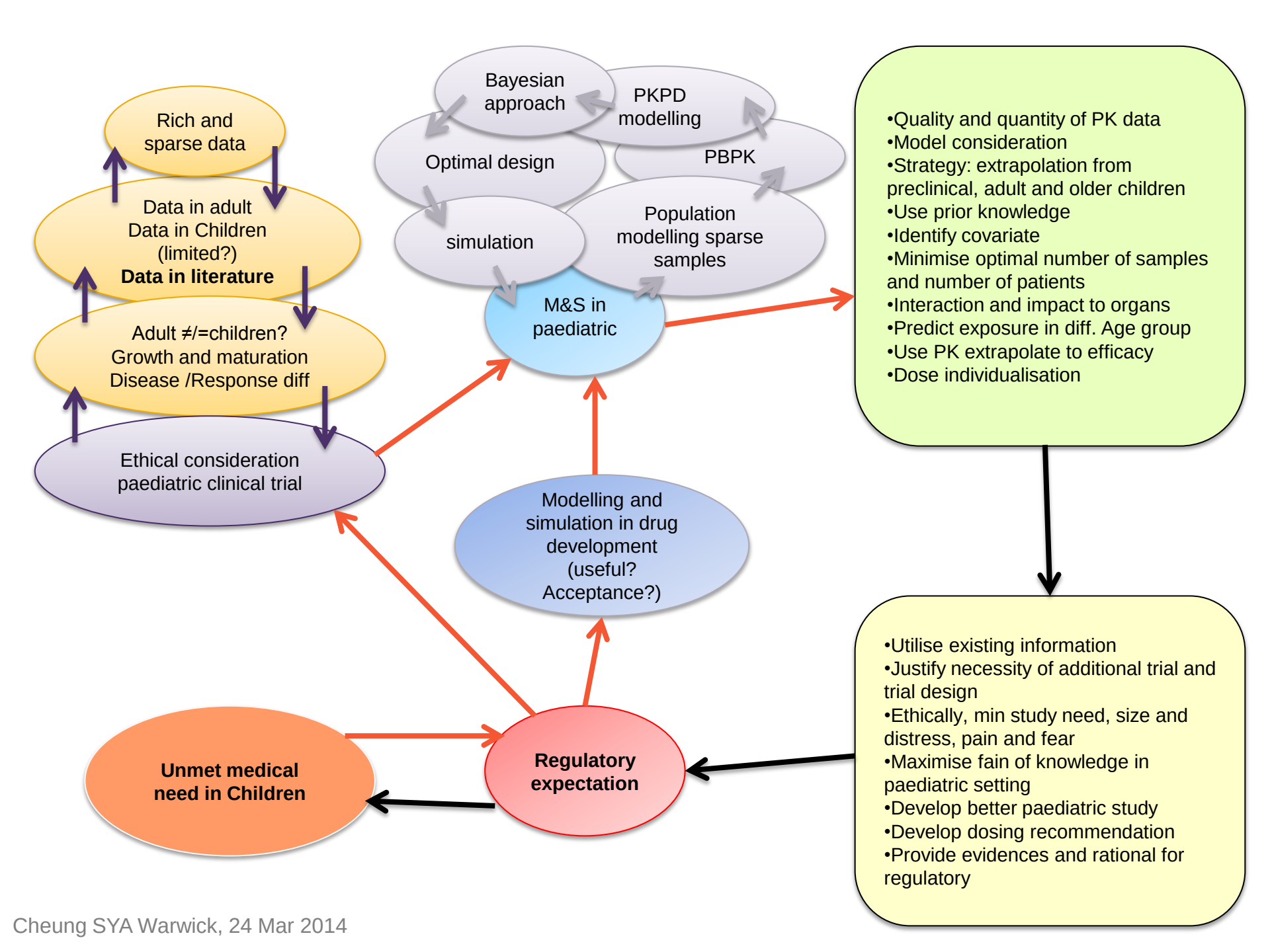


Adaptive trials in paediatric development: dealing with heterogeneity and uncertainty in pharmacokinetic differences in children

Massimo Cella,[1] Meindert Danhof[1] & Oscar Della Pasqua[1,2]

[1]LACDR, Division of Pharmacology, Leiden University, Leiden, The Netherlands and [2]Clinical Pharmacology and Discovery Medicine, GlaxoSmithKline, Stockley Park, UK

- Usefulness of simulation with existed model and data
- Incorporate ongoing study data for dose adjustment
- Adaptive design incorporation into protocol


Rich and sparse data
Data in adult
Data in Children (limited?)
Data in literature
Adult ≠/=children?
Growth and maturation
Disease /Response diff
Ethical consideration paediatric clinical trial
Bayesian approach
PKPD modelling
Optimal design
PBPK
simulation
Population modelling sparse samples
M&S in paediatric
•Quality and quantity of PK data
•Model consideration
•Strategy: extrapolation from preclinical, adult and older children
•Use prior knowledge
•Identify covariate
•Minimise optimal number of samples and number of patients
•Interaction and impact to organs
•Predict exposure in diff. Age group
•Use PK extrapolate to efficacy
•Dose individualisation
Modelling and simulation in drug development (useful? Acceptance?)
Unmet medical need in Children
Regulatory expectation
•Utilise existing information
•Justify necessity of additional trial and trial design
•Ethically, min study need, size and distress, pain and fear
•Maximise fain of knowledge in paediatric setting
•Develop better paediatric study
•Develop dosing recommendation
•Provide evidences and rational for regulatory

Conclusion

M&S → crucial decision → fewer trials →fewer failure compounds →reduce cost →higher productivity

Key → Integrating trials and external data as projects develop (base decision on evidence in data)

Literature → Some therapy areas are better represented in the literature than others using M&S

- Clinical end point (measured + sampled) e.g. pain
- System biology/pharmacology → cellular pathway e.g. oncology

Communication → Results to influence a project

Use and learn → existing tools

Adapts new tools → to the current process

Wider education → M&S idea

Collaboration→ Scientists and clinical practitioners

Impact→ Science and patient's life

Thank you and questions?

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