EMA EFPIA workshop
Break-out session no. 3

M&S as a tool to bridge PK, efficacy and safety data in special populations, ethnic groups and rare diseases

LEADING STATEMENTS

1. An **evidence-based approach is often unsuitable** for the evaluation of pharmacokinetics, pharmacodynamics, safety and efficacy in special populations, ethnic groups and rare diseases.

2. Inferential methods (M&S) should underpin evidence synthesis and knowledge integration in the development of drugs for special populations, ethnic groups and rare diseases

3. Inferences are required to support evidence synthesis during the **design stage (i.e., protocol optimisation)**, as well as during the **analysis and interpretation** of existing or new evidence.

4. The **consequences of M&S assumptions** must be assessed**.** Assumptions can be **violated** (this should be addressed accordingly e.g. by additional evidence or by a better model), **mitigated** (e.g., by label restriction, dose titration) or **pertain as risk** to patients and other stakeholders (e.g., regulator/sponsor).

Evidence Based Medicine

"Observations"

"Inferences"

Framework for M&S in regulatory review according to impact on regulatory decision

High impact

Scientific Advice **(+)** Documentation **(+++)**

Medium impact

Scientific Advice **(±)** Documentation **(++)**

Low impact

Scientific Advice **(-)** Documentation **(+)**

Impact on regulatory decision

Framework for M&S in regulatory review

High Impact

- Provide evidence of comparability (biosimilarity, biowaivers for MR formulations using IVIVC and in vitro data)
- Provide evidence of sensitivity of study design to detect and explain treatment differences.
- Extrapolation of efficacy and safety from limited data (e.g. term and preterm neonates, paediatrics, small populations)
- Model-based inference as evidence of efficacy/safety in lieu of pivotal clinical data
- Inferences key to benefit risk to inform SPC content in at least a subpopulation (i.e., extrapolation of efficacy and safety from limited data)

Scientific Advice (+) Documentation (+++)

Case Studies

We we will illustrate how M&S can be used as a management tool for evidence synthesis and how assumptions can be managed during drug development for special populations, ethnic groups and rare diseases. In these examples, focus will be given to the following ASSUMPTIONS :

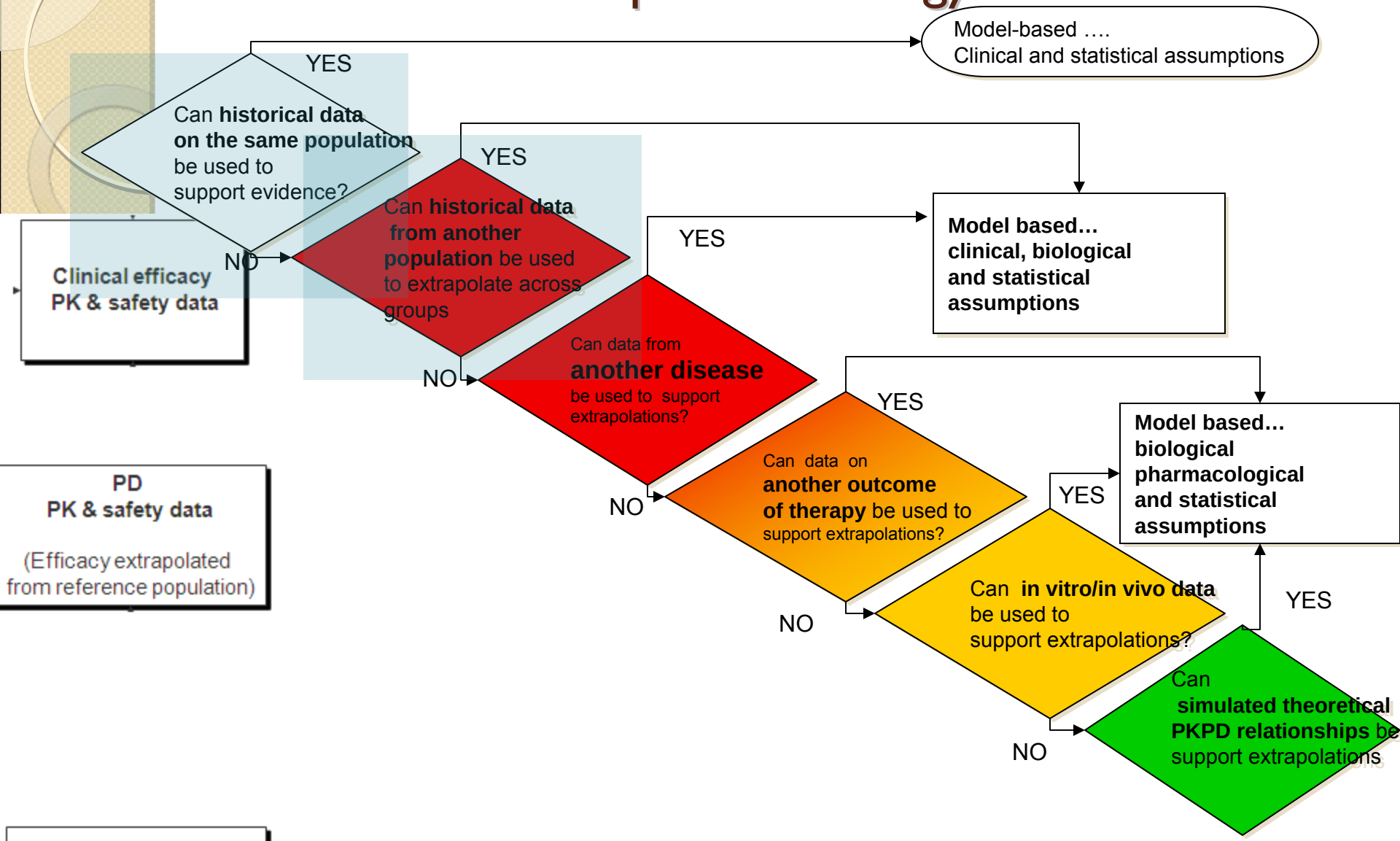
1.Use of historical data from a reference population under the assumption of ***scalable ADME processes***

2.Use of data from another disease (indication) under the assumption of ***comparable pathophysiology and PKPD relationship across populations***

3.Use of historical data from a reference population under the assumption of ***similar parameter-covariate relationships, no model misspecification***

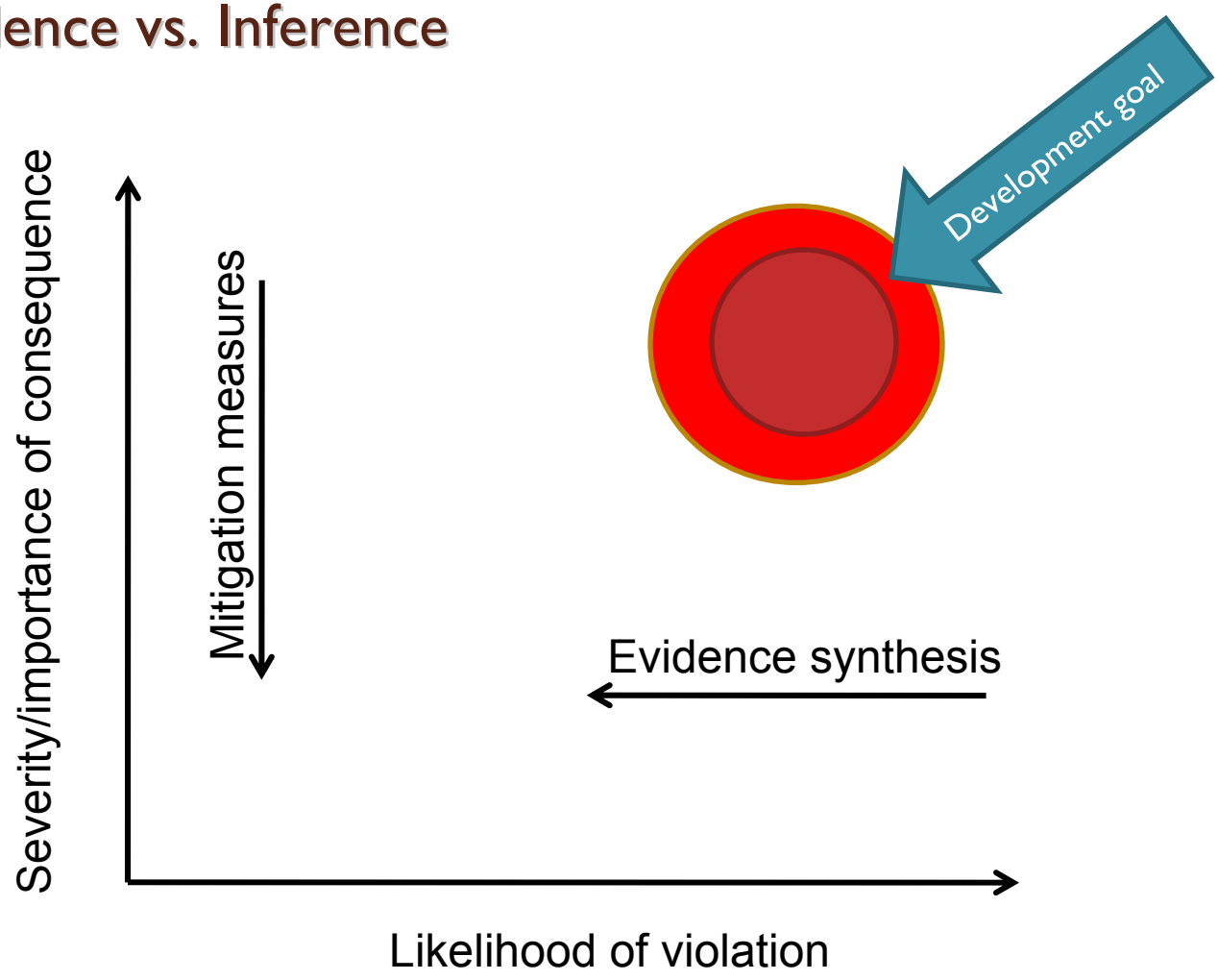
4.Use sparse data under the assumption of ***no model uncertainty and parameter precision***

Model-based development strategy



Impact of Assumptions

Evidence vs. Inference



BOS3: M&S as a tool to bridge PK, efficacy and safety data in special populations, ethnic groups and rare diseases

Assumption	Probability to violate	Clinical Consequences	Implications for evidence synthesis	Impact of M&S on development programme
PK properties	Definitely Likely Unlikely Improbable	Minor Major Unknown	No additional evidence required More evidence from large/small subset Accept risk if further evidence gathering is unfeasible	Reduce trial burden Reduce sampling frequency
PD properties	Definitely Likely Unlikely Improbable	Minor Major Unknown	No additional evidence required More evidence from large/small subset Accept risk if further evidence gathering is unfeasible	Incorporation of biomarkers Better dose rationale
Disease	Definitely Likely Unlikely Improbable	Minor Major Unknown	No additional evidence required More evidence from large/small subset Accept risk if further evidence gathering is unfeasible	Population selection Stratification Different recommendation (e.g., contraindication)
Patient population	Definitely Likely Unlikely Improbable	Minor Major Unknown	No additional evidence required More evidence from large/small subset Accept risk if further evidence gathering is unfeasible	Estimation of covariate effects Define appropriate inclusion criteria
Statistical aspects	Definitely Likely Unlikely Improbable	Minor Major Unknown	No additional evidence required More evidence from large/small subset Accept risk if further evidence gathering is unfeasible	Reduce sample size Higher statistical power Eliminate need for a study

Assumption Impact & Consequence

Assumption	Probability to violate (uncertainty)	Consequence	Potential M&S impact
	Based on biological/ pharmacological/clinical prior understanding	Needs to adjust for environmental condition	Generally depends on density of available data
AUC_{ped} = AUC_{adult} (assuming allometric scaling)	**likely (at design stage)**	**major (equal exposure assumption in stats analysis)**	**... allows regrouping ... PKPD-model to define EC90**
AUC_{ped} ~ AUC_{adult}	**unlikely (post readout)**	**moderate**	**... quantifies confounding factors**
CPX_{ped} ~ CPX_{adult} (clinic. meaningful effect size)	**moderate**	**moderate**	**... allows bridging <u>only</u> in conjunction with HDs**
$(CPX{\sim}HD)_{ped}$ = $(CPX{\sim}HD)_{adult}$	**unlikely**	**major**	**... qualifies bridging of CPX~HD EPs between populations**
DP_{ped} = Dp_{adults}	unlikely	moderate	... justifies design in SP
$HD\text{-}ER_{ped}$ = $HD\text{-}ER_{adults}$	unlikely	major	... justifies dose in children
$HD\text{-}ER_{<7y/non\text{-}able}$ = $HD\text{-}ER_{>7y/able}$	unlikely	major	... justifies dose in younger/non-able children
$HD\text{-}ER_{strata}$ = $HD\text{-}ER_{major\text{-}group}$	moderate	moderate	... quantifies dose for strata
$CPX\text{-}ER_{<7y/non\text{-}able}$ = $CPX\text{-}ER_{>7y/able}$	very likely	major	No existing data, → future research

"A one-sided significance level of 0.1 is applied for the statistical test of the primary outcome variable."

(One-sided significance levels up to 0.25 have been seen in the PDCO!)

If the extrapolation paradigm does not hold (**the treatment does not work in the subpopulation**) the risk of a false positive decision from the validation study remains as high as the significance level γ (=0.1) chosen for the validation study !

Scale of scepticism s

The *Scepticism Factor s* is the "probability" that the treatment is not effective in the sub-population, i.e. that the extrapolation assumption is incorrect.

mild — strong

No additional evidence necessary — Full evidence necessary

Sugammadex
(mechanistic extrapolation)

Topiramate
(dissimilar disease?)

Sildenafil in older children

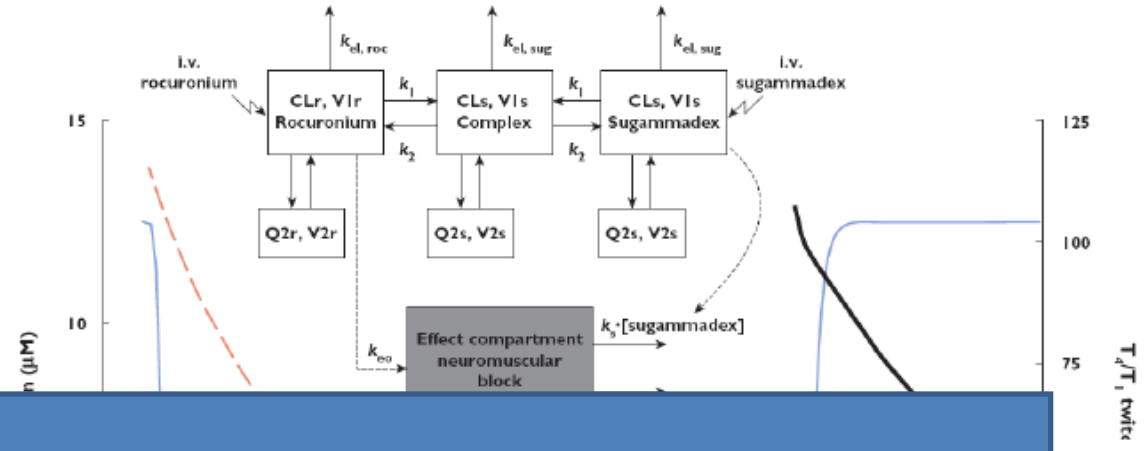
Sildenafil in younger children

Proguanil/Atoquavone

Ethnic differences in Japanese patients
(neuropathic pain)

Sugammadex

PK-PD model assumptions



High impact

Impact SPC, but substitutes for additional evidence

Might there data be needed to validate the assumptions?

ped by interaction

gammadex

(3) Free rocuronium drives PD. Encapsulated it is pharmacodynamically inactive

(4a) Allometric scaling by bodyweight of CL, V

(4b) Sugammadex CL driven by renal function

(5) PD model structure on literature data

(6) Allometric scaling PD rate constants, distribution effects cause PD delay. Enables faster reversal in pediatrics!

Special populations

Mean onset time in infants and children at an intubation dose of 0.6 mg/kg is slightly shorter than in adults. The duration of relaxation and the time to recovery tend to be shorter in children compared to infants and adults.

Topiramate (epilepsy)

2 yrs

6 yrs

10 yrs

Adjunct -therapy

Approved

Data

Mono-therapy

Approved

Data

Topiramate

- Bridging treatment to 2-10 years old children with Epilepsy
  - Data integration & evidence ”synthesis”
- Adjunct Approved in all children
  - Mono therapy only from beyond 10 years
  - No mono therapy data beyond 6 years old
  - Different EP in mono (TTFS) vs adjunct (%red SF)
  - PKPD on both EPs
  - Model cannot identify an effect of age or pediatric status therefore dose recommendation labelled

Topiramate

- “Reach a level of disagreement”
- Epilepsies in children
  - Most relevant epilepsies ignored, epilepsies which don’t exist in adults! No extrapolation possible for AE or PD
- The absence of an effect is ONLY VALID for POS and Lennox-Gastaud syndrome
- Need for a specific approach to infantile and juvenile epilepsies
- If level of scepticism is low, PK safety exploration sufficient
- FDA decision tree is not fully adequate in the most specific aspects of peds DD due to oversimplification

Negotiating on the scepticism level …

- Violating assumption
  - Accept underlying risk
    - Quantify consequences
  - Mitigate against risk
    - Label restrictions
    - Provide additional evidence
      - Internal (new sponsor's data)
      - External (stakeholder's data, integrated models)

What is required for future use of model-based approaches (tools and methods)?

- For the purpose of Bridging, extrapolation, translation

- Understanding of CP is of most importance
  - Not just theoretical evidence
- A much larger need for mechanistic models
- PBPK and PBPK-PD modelling
- Learning, checking, confirming
- What to do if important deviations appear? Adaptation

- Obtain data from observational studies, to share among stakeholders (Pharma, Academics), encouraged by PDCO
- Standardize and aggregate data

Sample size estimation for a paediatric clinical trial utilising external information from historical trials in adults and children

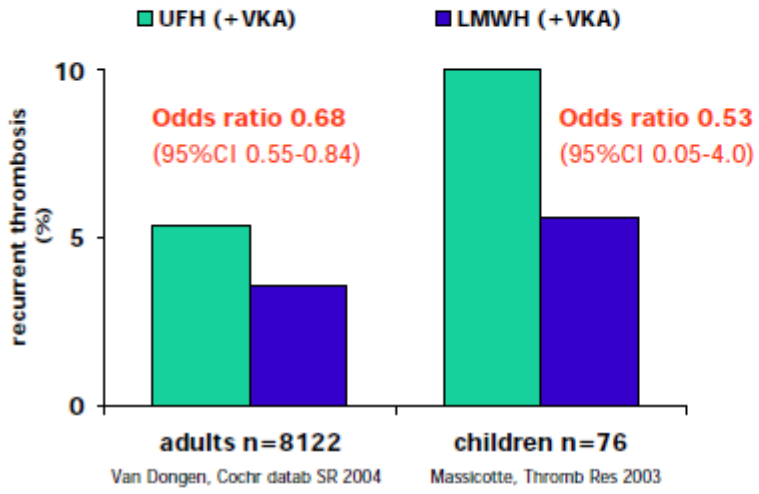
- Determine the amount of evidence that historical data could contribute to a future trial
- Existing data of 8122 adult plus 76 paediatric patients (=8198 patients in total) equates to 116 “virtual subjects” (small to moderate variability)
- With Bayesian modelling it is possible to use external historical information for planning a new study

Prior log Odds Ratio	-	-0.6514 ± 0.9373	-0.6514 ± 0.9373
Prior effective sample size	-	116	116
Expected Event Rate (Intervention group)	5.56%	5.56%	5.56%
Expected Event Rate (Control group)	10%	10%	10%
Sample size in new trial (total)	580	468	580
Bayesian Power (simulated)	0.8016	0.8017	0.8757

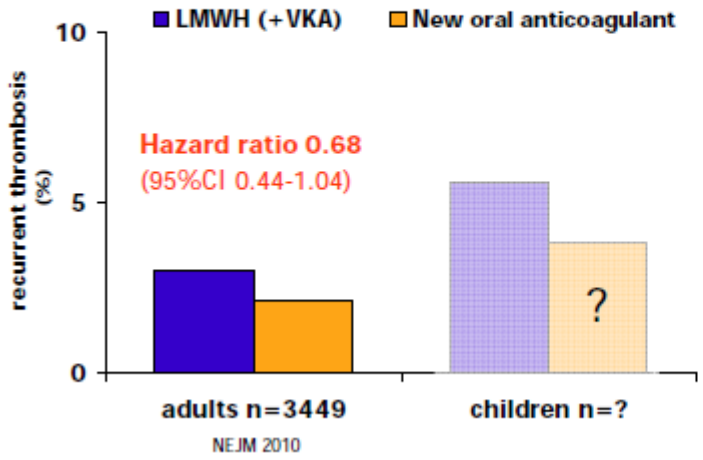
Future perspective

Extrapolation for new oral anticoagulant

Historical data



New anticoagulant



Paediatric Investigation Plan for new oral anticoagulant:

- PBPK-modelling
- In-vitro concentration-response
- PK/PD studies
- Efficacy & safety RCT, 3 mo VTE treatment, sample size ?