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PBPK MODELING OF PROPOFOL USING THE MIDDLE OUT APPROACH

Outline

- Scope
- What is propofol?
- PBPK modeling (bottom-up)
- PopPK modeling (top-down)
- Retrograde PBPK modeling (middle-out)
- Model verification
- Conclusions

Scope: Paediatric drug development

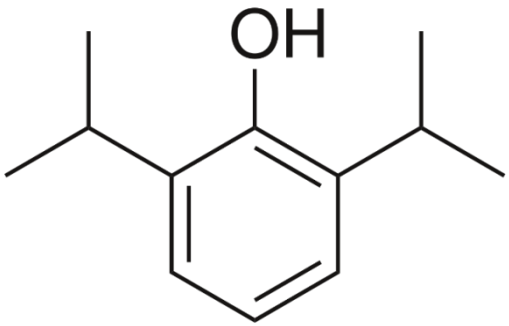
- 50-90% of medication used off-label in children
- However, clinical trials in children are hard, rare and yield less data (sparse sampling)

➔Need for a new framework to design, develop, test and evaluate paediatric drugs

➔SAFEPEDRUG Project: develop this framework using **model compounds** with specific characteristics

What is propofol?

- Small and lipophilic
  - V_d estimated at 300L - 4000L
- Context-sensitive half-life
- **Rapidly** and **extensively** metabolised: less than 0.3% of the dose is excreted unchanged
  - Clearance blood flow limited
  - Occurs in **multiple organs**
  - Both **CYP and UGT**



PBPK MODELING (BOTTOM-UP) OF PROPOFOL

Constructing a pediatric PBPK model

Adult PBPK model

- Build bottom-up from *in vitro* kinetic data (Km, Vmax, CLint)
- Estimate PK parameters (Clearance, Volume of distribution)
- Sensitivity analysis, clinical trial simulation (to gain confidence)
  → Validate model against adult *in vivo* data

Switch adult to paediatric population

- Account for:
  ontogeny of enzymes/transporters, tissue volumes,
  tissue composition, blood flow
  (Same drug specific factors, different population data)

Paediatric PBPK model

- Evaluate paediatric PBPK model predictions against
  - observed pediatric *in vitro* kinetics and
  - observed pediatric *in vivo* data

Previous work: Gill et al.

Gill, K. L., Gertz, M., Houston, J. B., and Galetin, A., "Application of a physiologically based pharmacokinetic model to assess propofol hepatic and renal glucuronidation in isolation: utility of in vitro and in vivo data.," *Drug Metab. Dispos.*, vol. 41, no. 4, pp. 744–753, Apr. 2013.

- PBPK model based on *in vitro* experiments using human liver and kidney microsomes
- Severe underprediction of the *in vivo* clearance: +/- 30 L/h instead of +/- 100 L/h
- Completely attributed to underprediction of the glucuronidation (*in vitro* CL_{int} too low)
- Use of a scaling factor of 9 for hepatic glucuronidation CL_{int} and 17 for renal glucuronidation CL_{int} based on clinical data

In vitro metabolism experiments

Experiment	Parameter derived	Value (RSE)
HLM/HKM	Liver $CL_{int,CYP}$	70.33 (20%) µl/min/mg protein
	Liver $CL_{int,UGT}$	270 (12%) µl/min/mg protein
	Kidney $CL_{int,UGT}$	1270 (14%) µl/min/mg protein
Inhibition	Contributions CYP2B6 and CYP2C9	**CYP2B6: 4.13%** CYP2C9: 12.5 %
Recombinant Systems	$CL_{int,CYP2B6}$	**2.5 (19%)** µl/min/pmole CYP
	$CL_{int,CYP2C9}$	0.93 (23%) µl/min/pmole CYP
	$CL_{int,UGT1A9}$	350 (15%) µl/min/pmole UGT

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Low activity CYP2B6 in HLM

Activity Adjustment Factor CYPs

- To correct for differences in HLM batch-specific activity
- Comparison bupropion (CYP2B6) and diclofenac (CYP2C9) *in vitro* CL_{int} with scaled back CL_{int} from clinical data
- AAF CYP2C9: 0.65
- AAF CYP2B6: 67.3

➔ Explains low contribution CYP2B6

PBPK models

Model	$CL_{IV,Ref}$ (L/h)	%CYP2B6	%CYP2C9	%UGT1A9, liver	%UGT1A9, kidney
Pure PBPK (B:P and f_u Gill et al.)	23.94	0.98%	2.96%	58.29%	24.94%
Pure PBPK (B:P and f_u predicted)	64.81	0.93%	2.81%	55.39%	28.68%
$PBPK_{AAF}$ HLM	80.37	40.15%	1.17%	35.55%	23.12%

Reference individual: 25 years old, 80 kg

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PBPK model results

- "Best" predicted CL_{IV}: 80.37 L/h
- Large variation of reported clearance in literature:
  61.2 - 97.8 L/h (Morgan et al., 1990),
  87.6 L/h (Smuszkiewicz et al., 2016),
  110 L/h (Eleveld et al., 2014)

- Can be caused by trial conditions:
  - Long infusions ➔ accumulation in fat
  - Short sampling time ➔ underprediction CL

➔ Combine available data to provide "benchmark CL_{IV}"

POPPK MODELING (TOP-DOWN) OF PROPOFOL

Earlier work and available data

	Morgan et al.	Smuszkiewicz et al.	Eleveld et al.
N	9	29	660
T_{inf}	2 – 10 h	100 – 220 h	< 1 h
T_{sample}	24 – 120 h	8 h	2 – 15 h
CL_{IV}	75.3 L/h	87.6 L/h	109.8 L/h
V_d	2920 L	955.1 L	239.5 L
$t_{1/2}$	29.9 h	7.7 h	1.5 h

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Parameter	Value	(SE) (range)
CL_{IV} (CL_1)	86.40 L/h	10% (9-12%)
V_d ($V_1 + V_2 + V_3$)	976 L	15% (13-16%)

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PBPK CL_{IV} : 80.37 L/h < PopPK CL_{IV} : 86.40 L/h

PBPK V_d : 1288 L > PopPK V_d : 976 L

RETROGRADE PBPK MODELING (MIDDLE-OUT) OF PROPOFOL

Retrograde clearance calculation

- Total CL_{IV} calculated back to hepatic and renal CL_{int} for reference individual
  - CYP and UGT fractions
  - Renal and hepatic fractions

➔ *In vivo* literature data needed

In vivo data used

Parameter/fraction	Value	Source
Total CL_{IV}	86.40 L/h	popPK model
$f_{m,UGT}$	62%	Favetta et al., 2002
$f_{m,CYP}$	38%	Favetta et al., 2002
CYP2B6 contribution	$CL_{2B6,EM}/CL_{2B6,PM}$ = 2.66	Eugene et al., 2017
Renal contribution	33.3%	Raoof et al., 1998, Gill et al., 2013, Veroli et al., 1992
Hepatic contribution	66.7%	Assumed to be 100% - renal contribution

Retrograde clearance calculation: $CL_{H,CYP}$

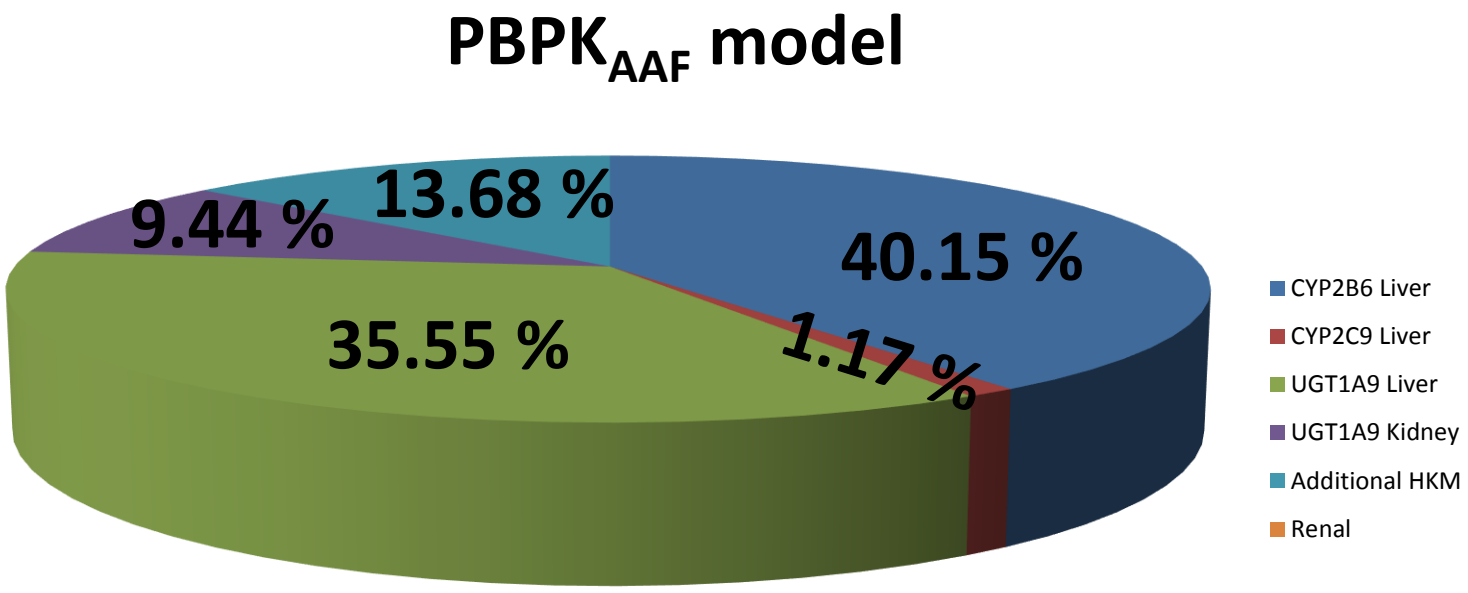
- Start: $CL_{H,CYP}$ → 38% (no CYP in kidneys) of 86.92 L/h = 32.83 L/h
- $CL_{H,tot}$ = 66.7% (2/3 metabolism in liver) of 86.92 L/h = 57.63 L/h
- Build PM and EM population
- Back calculation in Simcyp® using retrograde enzyme kinetics module and varying 2B6 contributions (and multiplying with 32.83/57.63 to maintain hepatic CYP metabolism) until $CL_{IV,EM}/CL_{IV,PM}$ = 2.66

  → 94% CYP2B6 and 6% CYP2C9

Retrograde clearance calculation: CL_{UGT}

- No retrograde calculator available for UGTs
- Vary $CL_{int,UGT}$ until CL_H = 57.63 L/h
  - ➔ $CL_{int,UGT}$ = 243 µl/min/pmole UGT
- Different $CL_{int,UGT}$ needed for kidney and liver. Vary rUGT scalar until all enzyme contributions are equal to *in vivo* values.
  - ➔ rUGT scalar for kidney = 12.8

Retrograde clearance calculation: $CL_{Tot,IV}$



PBPK$_{AAF}$ model

$CL_{Tot,IV}$ = 80.37 L/h

$\%CL_{CYP}$ = 41%, $\%CL_{UGT}$ = 59%

$\%CL_H$ = 77%, $\%CL_R$ = 23%

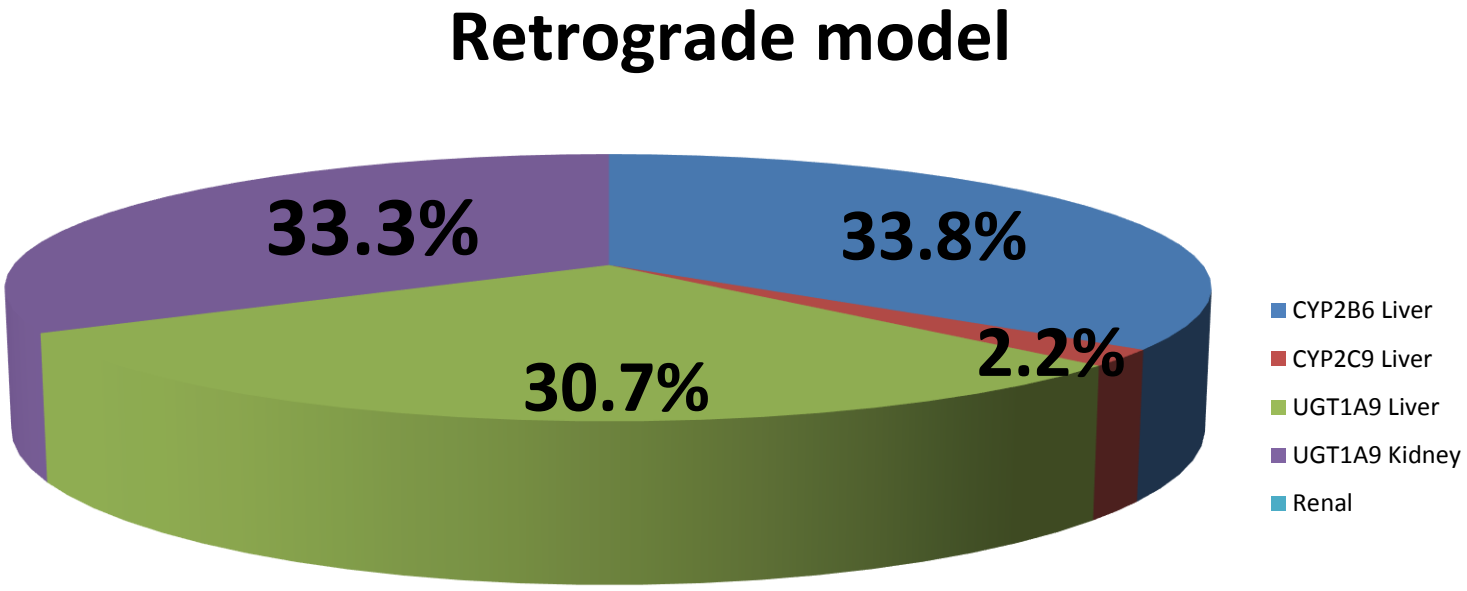
In vivo

$CL_{Tot,IV}$ = 86.40 L/h

$\%CL_{CYP}$ = 38%, $\%CL_{UGT}$ = 62%

$\%CL_H$ = 66.7%, $\%CL_R$ = 33.3%

Retrograde clearance calculation: $CL_{Tot,IV}$



RG model

$CL_{Tot,IV}$ = 86.90 L/h

$\%CL_{CYP}$ = 36%, $\%CL_{UGT}$ = 64%

$\%CL_H$ = 67%, $\%CL_R$ = 33%

In vivo

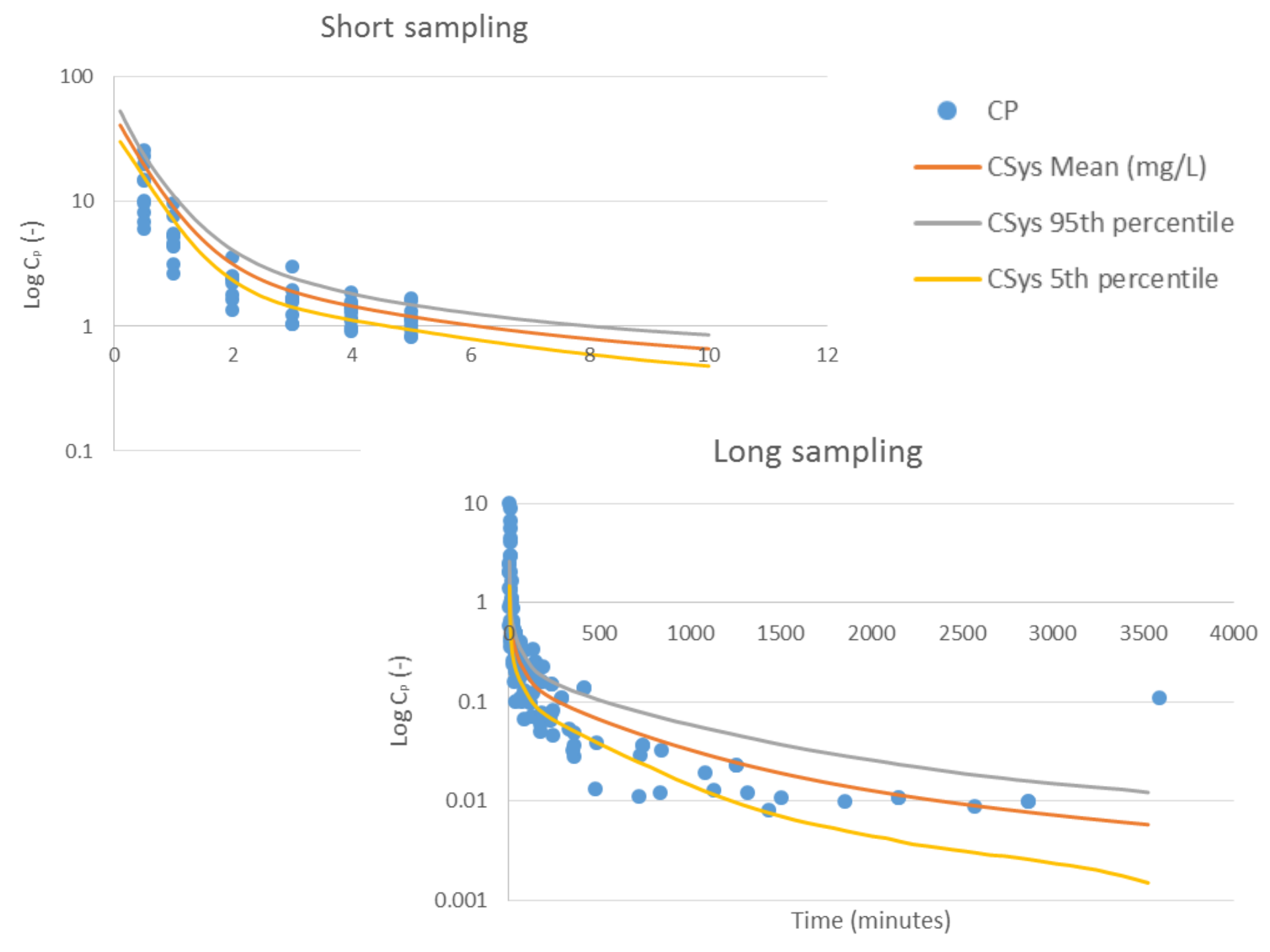
$CL_{Tot,IV}$ = 86.40 L/h

$\%CL_{CYP}$ = 38%, $\%CL_{UGT}$ = 62%

$\%CL_H$ = 66.7%, $\%CL_R$ = 33.3%

Model verification: CTS

- 2 real trials simulated
  - 2.5 mg/kg bolus to 10 women (22y-48y), 5 minutes intense sampling
  - 2.5 mg/kg bolus to 10 individuals (19y-62y), 24-60h sampling
- 90% PI after simulating trial 100 times plotted over real data


Short sampling
100
10
1
0.1
Log Cp (-)
0
2
4
6
8
10
12
CP
CSys Mean (mg/L)
CSys 95th percentile
CSys 5th percentile
Long sampling
10
1
0.1
0.01
0.001
Log Cp (-)
0
500
1000
1500
2000
2500
3000
3500
4000
Time (minutes)

CONCLUSIONS

Conclusions

Retrograde model

- Perfect description of clearance
- (Adult) *in vivo* data required
- Best to extrapolate existing adult drugs to paediatrics

$PBPK_{AAF}$

- Adequate description of clearance
- (Trustworthy) *in vitro* data required
- Best approach for new molecules with limited *in vivo* data

Both powerful, complementary methodologies that can work in tandem depending on available data

SAFE-PEDRUG Project

Integrating multidisciplinary translational bottom-up approaches towards a new paradigm for paediatric investigations: the next step in ethical paediatric drug research

IWT-SBO PROJECT WITH A PRIMARY SOCIAL FINALITY