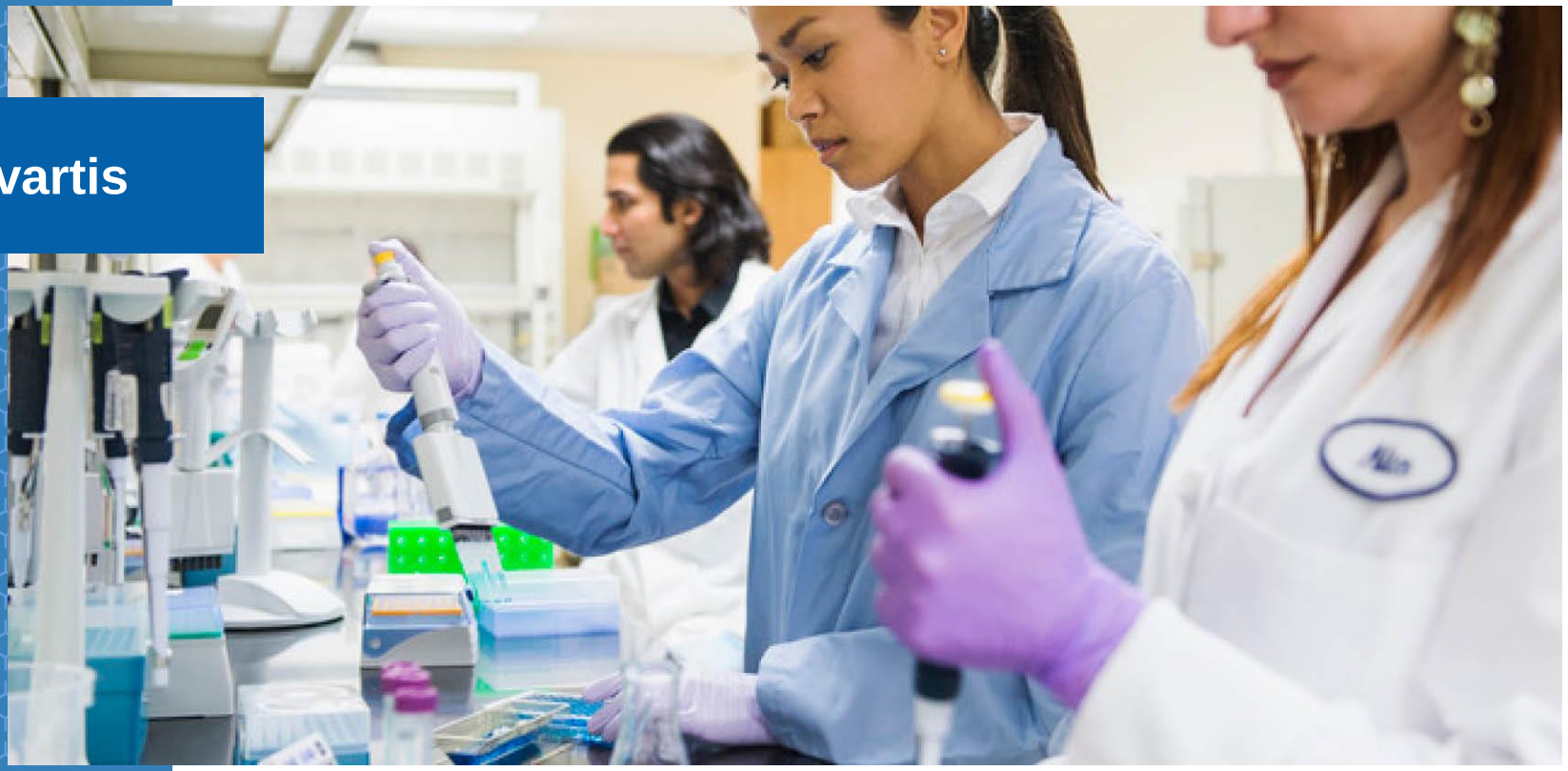
Novartis



Drug disposition classification systems:
A comparative review of BDDCS, ECCS and ECCCS

Birk Poller, Gian Camenisch - Novartis

SOLVO - Meet The Experts Transporter Conference

April 26, 2018

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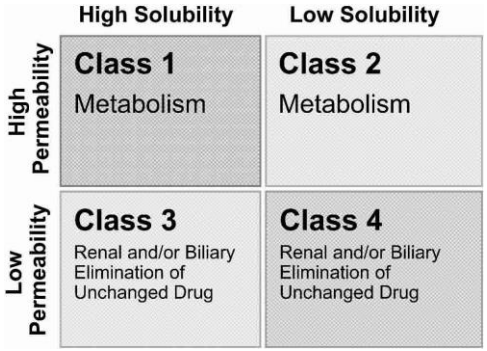
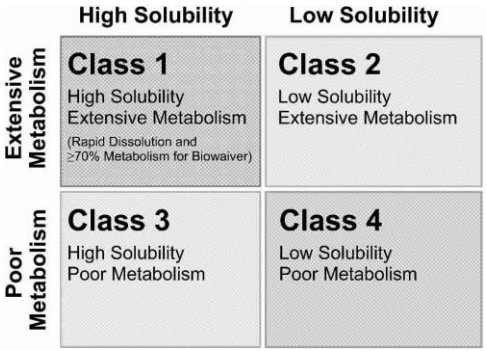
Drug disposition classification systems

BCS



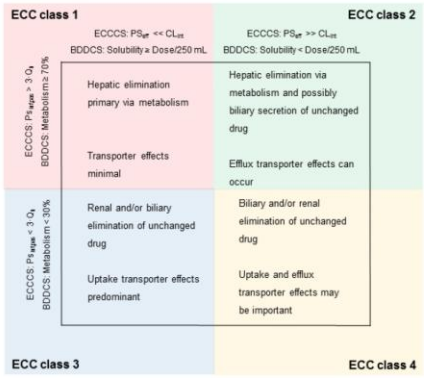
Amidon et al, 1995, Pharm Res;12:413-20

BDDCS



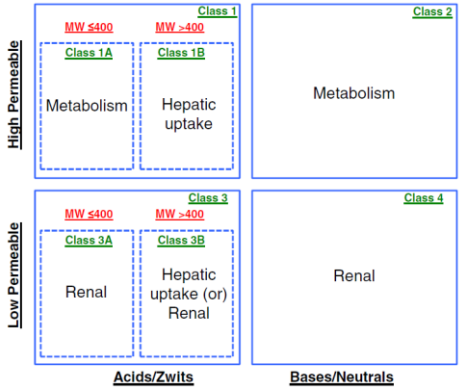
Wu and Benet, 2005, Pharm Res;22:11-23

ECCCS



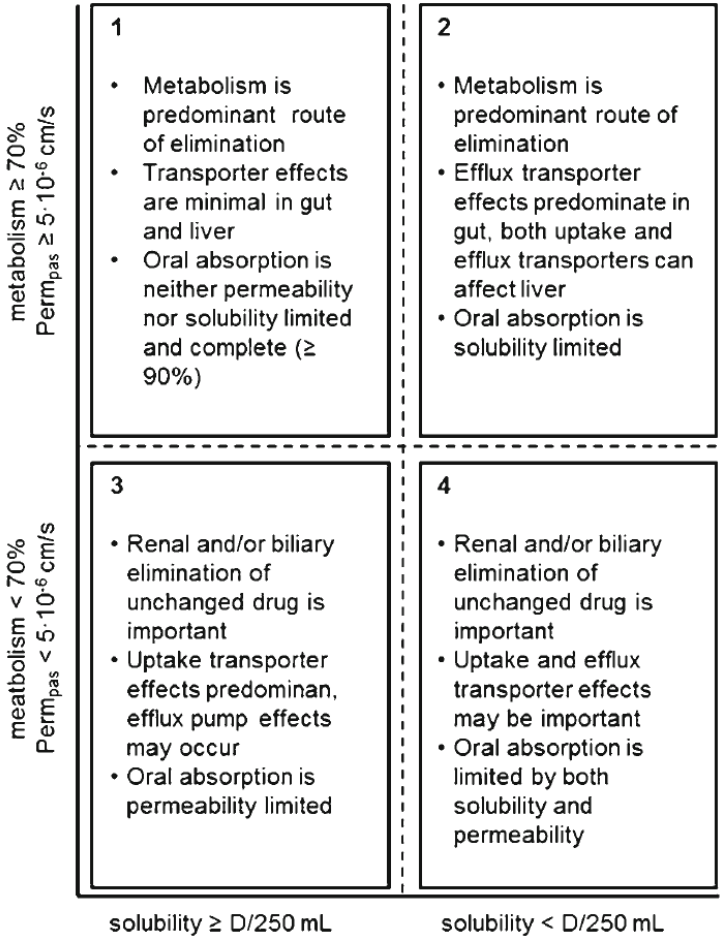
Camenisch et al, 2015, ADMET&DMPK;1:1-14
Camenisch, 2016, Pharm Res;33:2583-93

ECCS



Varma et al, 2015, Pharm Res;32:3785-802

Biopharmaceutics Drug Disposition Classification System (BDDCS)



Classification based on human *in vivo* metabolism (or passive permeability) and soluble dose

→ *Rather applicable in late drug development phases*

→ *Provides information about involvement of potential transport processes in absorption and elimination*

→ *Observation based classification system*

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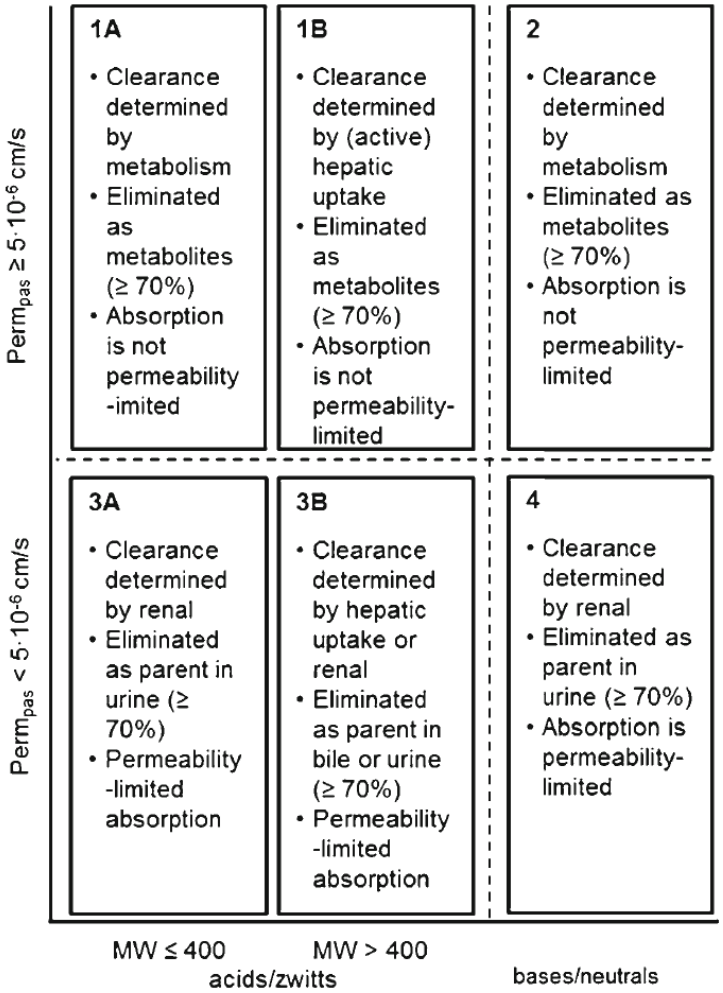
Extended Clearance Classification System (ECCS)



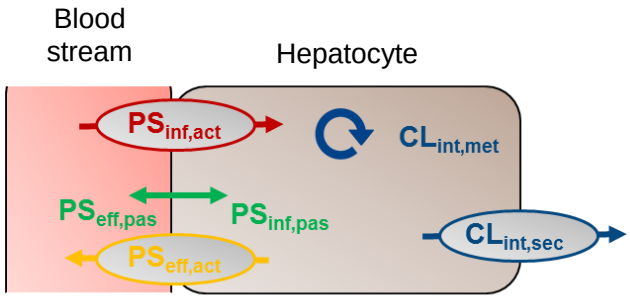
Classification based on *in vitro* permeability and physicochemical properties (MW, charge)

→ *Applicable in early drug development phases*

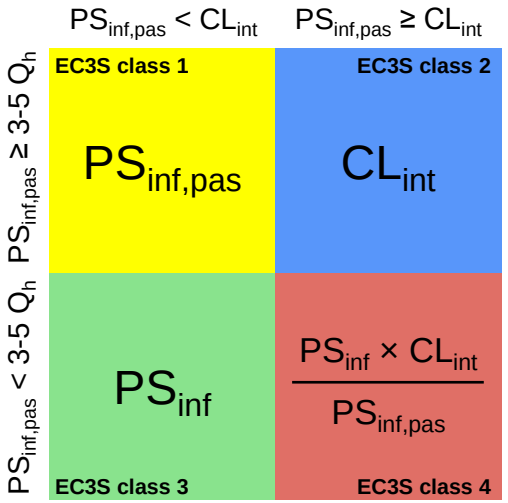
→ *Allows to identify the rate-limiting clearance processes (absorption, distribution and elimination model)*

→ *Observation based classification system (based on the extended clearance concept)*

Extended Clearance Concept Classification System (ECCCS = EC3S)



$$CL_{h,int} = \frac{PS_{inf,act} + PS_{inf,pas}}{PS_{eff,act} + PS_{eff,pas} + CL_{int}} \times CL_{int}$$

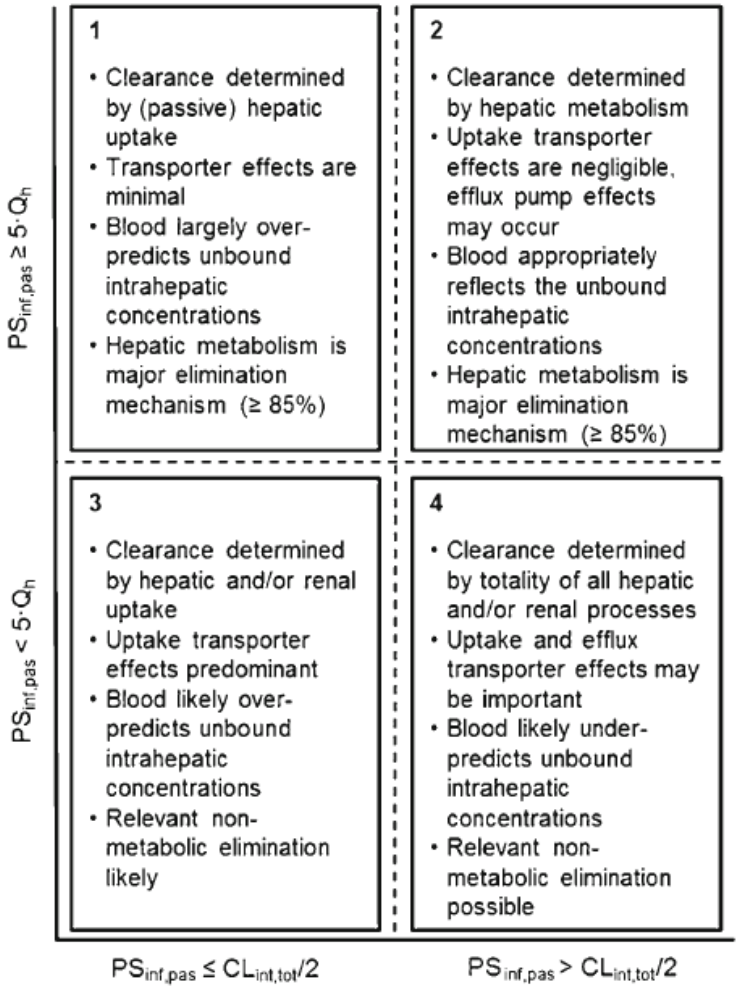


***in vitro* input parameters**

$PS_{inf,pas}$	Hepatic uptake / MDCK permeability
$PS_{inf,act}$	Hepatic uptake
$CL_{int,met}$	Liver microsomes / Hepatocytes / S9
$CL_{int,sec}$	Sandwich-cultured hepatocytes
$PS_{eff,act}$	= $PS_{inf,pas}$

Camenisch, 2016, Pharm Res;33:2583-93;
Shitara et al, 2005, Annu Rev Pharmacol Toxicol;45:689-723
Sirianni and Pang, 1997, J Pharmacokinet Biopharm;25:449-70

Extended Clearance Concept Classification System (ECCCS = EC3S)



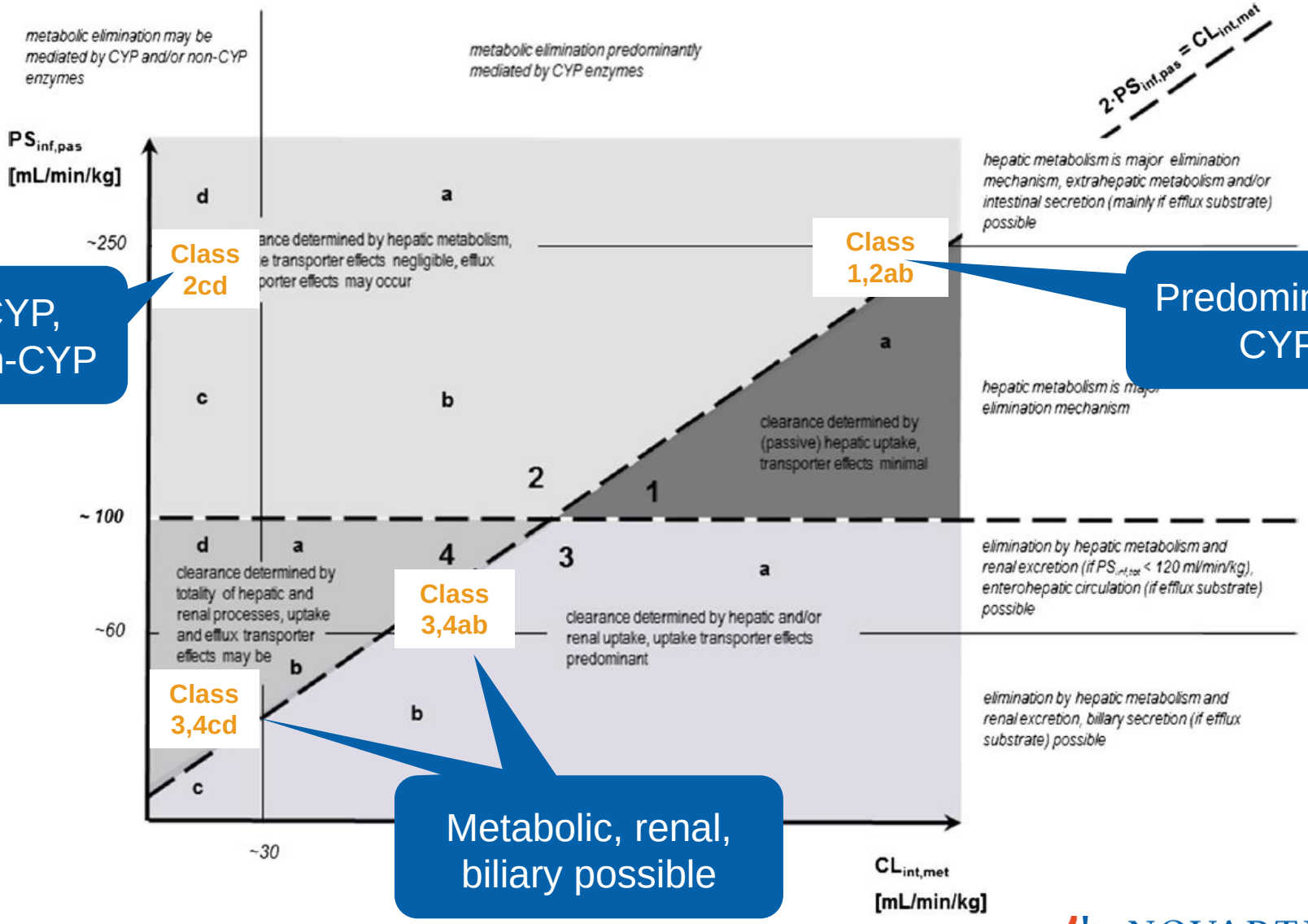
Classification based on *in vitro* permeability and *in vitro* metabolic and biliary clearance data

→ *Allows to identify the rate-limiting clearance processes (absorption, distribution and elimination model)*

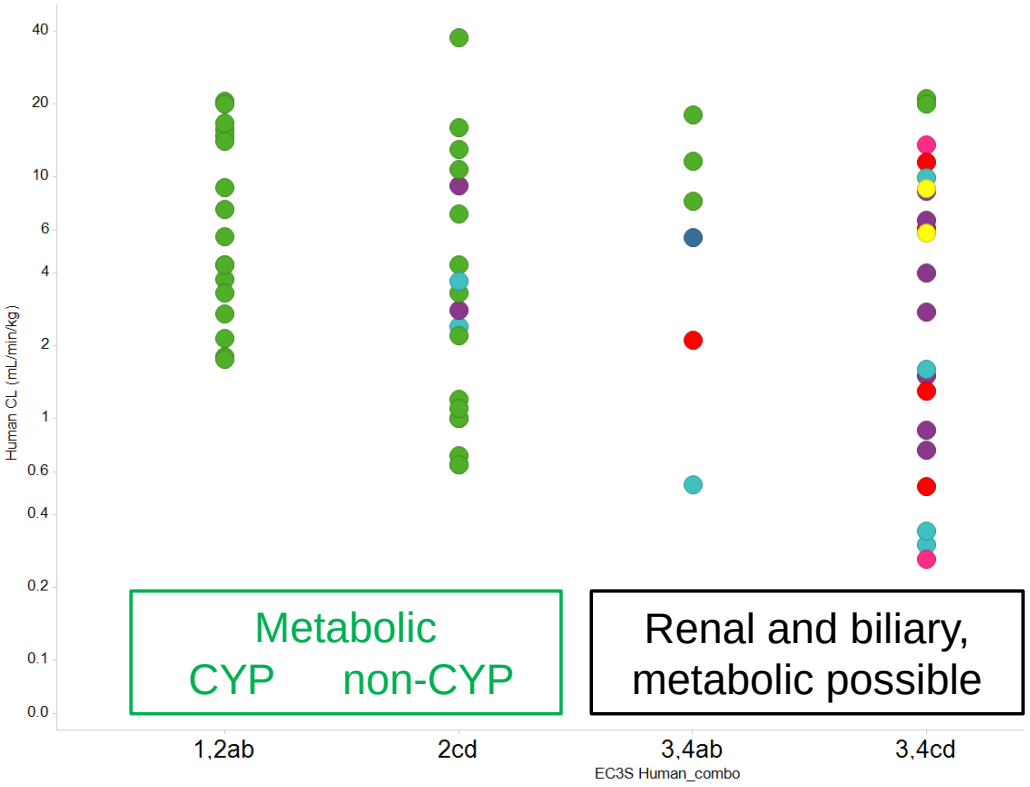
→ *Rate-limiting step of hepatic elimination*

→ ***Model-based drug absorption, distribution and elimination drug classification system***

EC3S – Elimination mechanisms



EC3S – Elimination mechanisms



Assessment based on ~80 Novartis compounds

Using **MDCK permeability** and **human liver microsomal stability** data for compound classification

- Metabolic elimination generally well predicted (MDCK-LE P_{app} > $5 \cdot 10^{-6}$ cm/s)
- EC3S provides information for CYP (Class 1,2ab) vs non-CYP (class 3,4ab)

→ Prediction of major elimination mechanisms in early development phase

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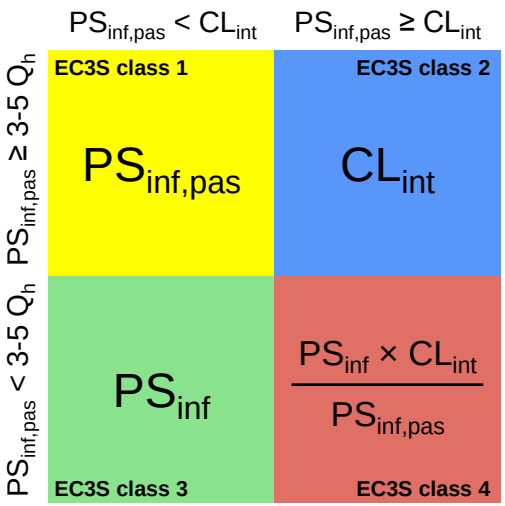
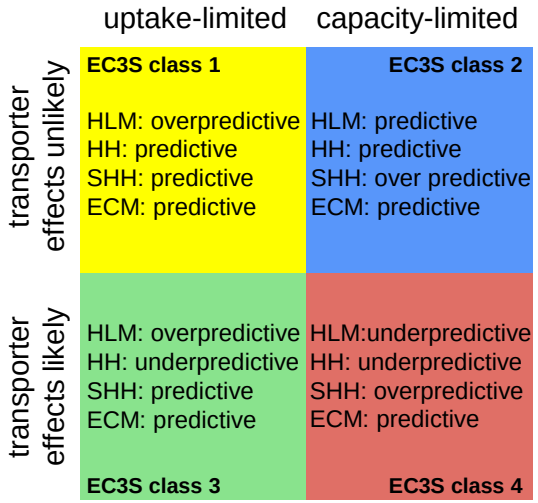
EC3S – Hepatic clearance IVIVE

Rate-determining process



liver



Hypothesis: knowing the rate-limiting process of hepatic elimination will facilitate selection of the most predictive clearance prediction tool

EC3S – Hepatic clearance IVIVE

Mechanism:	**In vitro assay:**
sinusoidal influx/efflux	suspended hepatocytes (**SHH**)
metabolism	liver microsomes (HLM), hepatocytes (**HH**)
biliary secretion	sandwich-cultured hepatocytes (**SCH**)
Extended Clearance Model (**ECM**)	HLM, SHH, SCH
plasma protein binding	ultrafiltration, ultracentrifugation or or equilibrium-dialysis

$$CL_{int,all} = CL_{met,u}$$

HH, HLM

$$CL_{int,all} = PS_{inf}$$

SHH

$$CL_h = Q_h \cdot E_h = \frac{Q_h \cdot f_{u,b} \cdot CL_{int,all}}{Q_h + f_{u,b} \cdot CL_{int,all}}$$

$$CL_{int,all} = \frac{PS_{inf} \times (CL_{sec,u} + CL_{met,u})}{PS_{inf,pas} + (CL_{sec,u} + CL_{met,u})}$$

ECM

$$CL_{int,all} = \frac{PS_{inf} \times CL_{met,u}}{PS_{inf,pas} + CL_{met,u}}$$

ECM (-)

→ **Expectation: different outcomes depending on rate-limiting clearance mechanism (EC3S class-dependent)**

Umehara and Camenisch, 2012, Pharm Res;29:603-17.
Camenisch and Umehara, 2012, Biopharm Drug Dispos;33:179-94.

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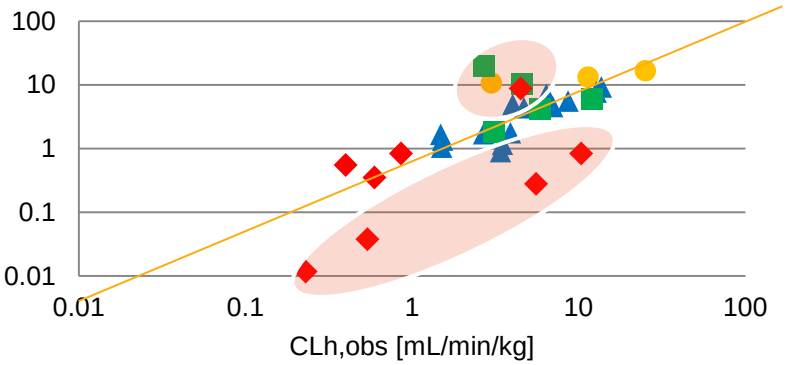
EC3S – Hepatic clearance IVIVE

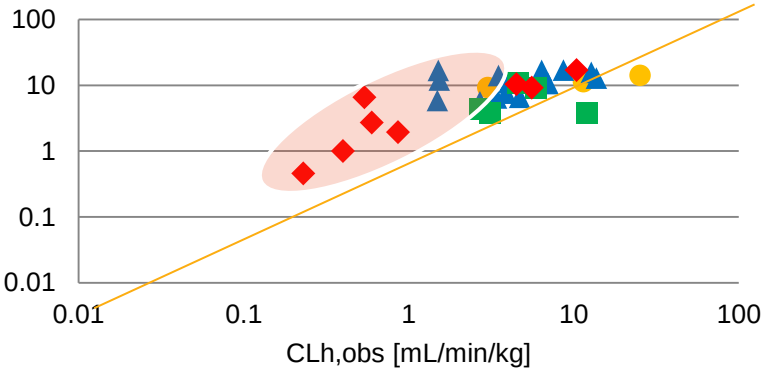
HLM:



$$CL_{int,all} = CL_{met}$$

→ Class 2 generally well predicted
→ Often under-predictive for class 4
→ Tendency for being over-predictive for class 1 and class 3

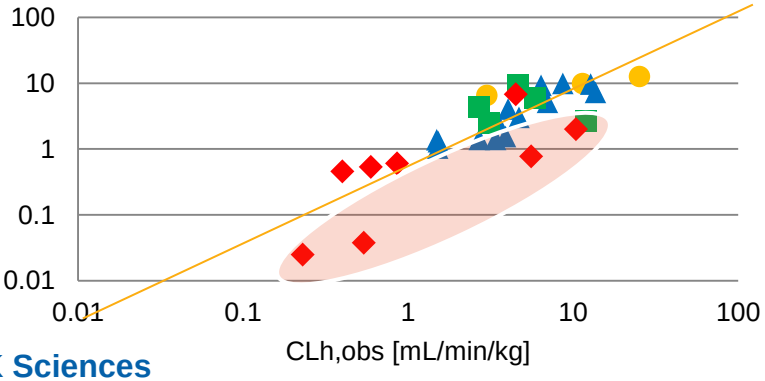
SHH



$$CL_{int,all} = PS_{inf}$$

→ Class 1 and class 3 generally well predicted
→ Over-predictive for some class 2 and class 4 cpds

ECM (-):



$$CL_{int,all} = \frac{PS_{inf} \times CL_{met}}{PS_{inf,pas} + CL_{met}}$$

→ Class 1, class 3 and class 2 generally well predicted
→ Under-predictive for some class 4 cpds

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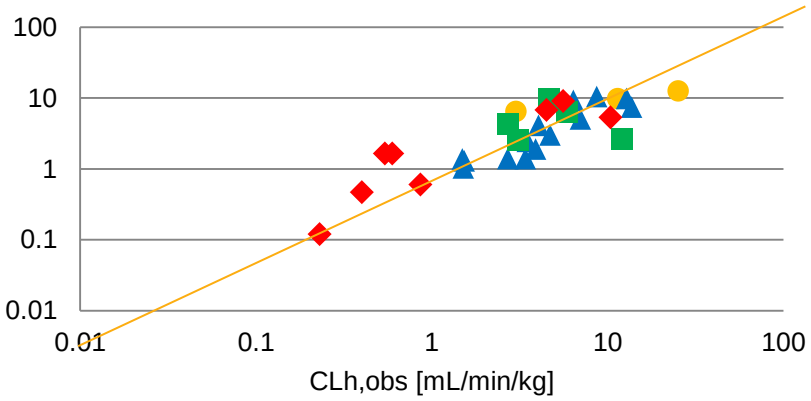
EC3S – Hepatic clearance IVIVE

ECM:



$$CL_{int,all} = \frac{PS_{inf} \times (CL_{sec} + CL_{met})}{PS_{eff} + (CL_{sec} + CL_{met})}$$

→ **Predictive for all EC3S classes**

IVIVE recommendations:

- **HH** is the method of choice for IVIVE of EC3S **class 1** cpds
- **HLM** or **HH** is the method of choice for IVIVE of EC3S **class 2** cpds
- **SHH** is recommended for EC3S **class 3** cpds (**HH** is the best alternative)
- **ECM** is needed for EC3S **class 4** cpds (no real alternative available)

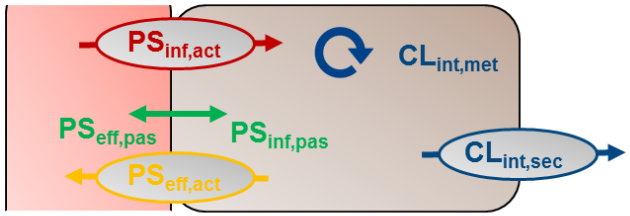
Camenisch et al, 2015, ADMET&DMPK; 3:1-14

EC3S – Total Clearance IVIVE

Estimation of fractional hepatic elimination

Total drug clearance (CL_{tot})

= hepatic drug clearance (CL_h) + renal drug clearance (CL_{ren})



Extended Clearance Model

?

no appropriate renal *in vitro* model available

→ **Is it possible to estimate relative contributions of hepatic (fn_h) and non-hepatic elimination pathways?**

$$CL_{tot} = \frac{CL_h}{fn_h}$$

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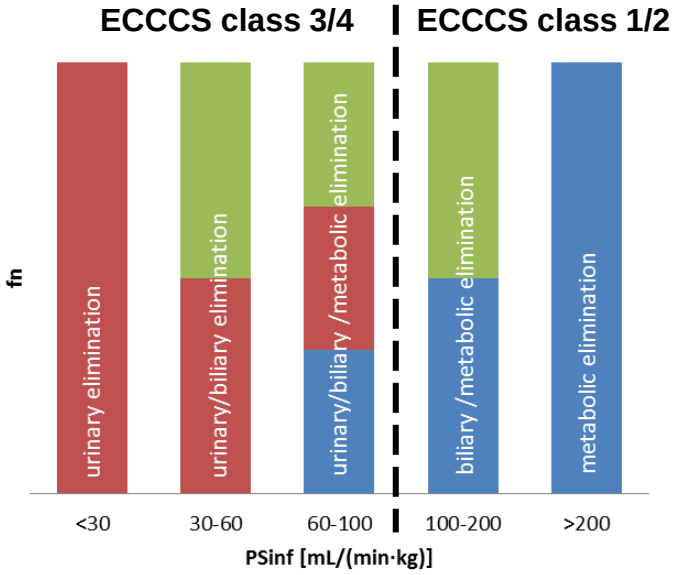
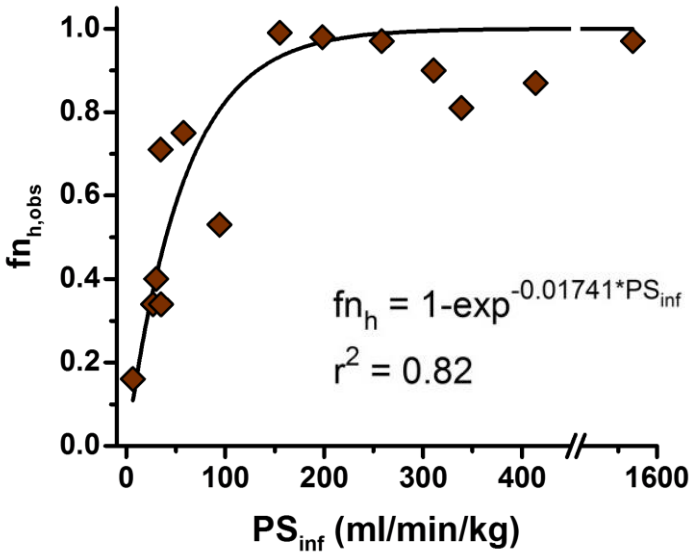
EC3S – Total Clearance IVIVE

Estimation of fractional hepatic elimination

Observation: hepatic uptake permeability correlates with elimination pathway





$$1 = fn_{ren} + \underbrace{fn_{sec} + fn_{met}}_{fn_h}$$

Camenisch et al, 2015, ADMET&DMPK; 3:1-14
Riede et al, 2016, Eur J Pharm Sci;86:96-102.

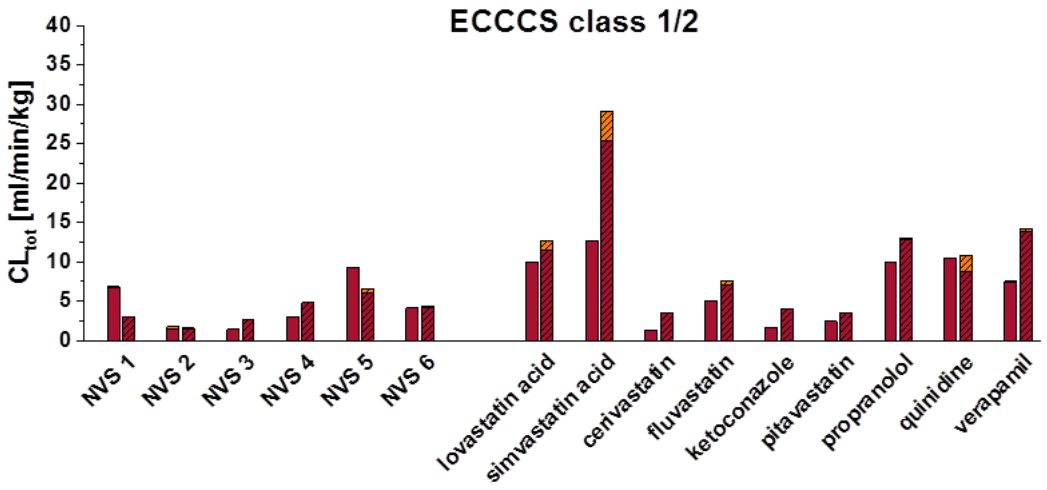
EC3S – Total Clearance IVIVE

Estimation of fractional hepatic elimination

ECCCS class 1/2:

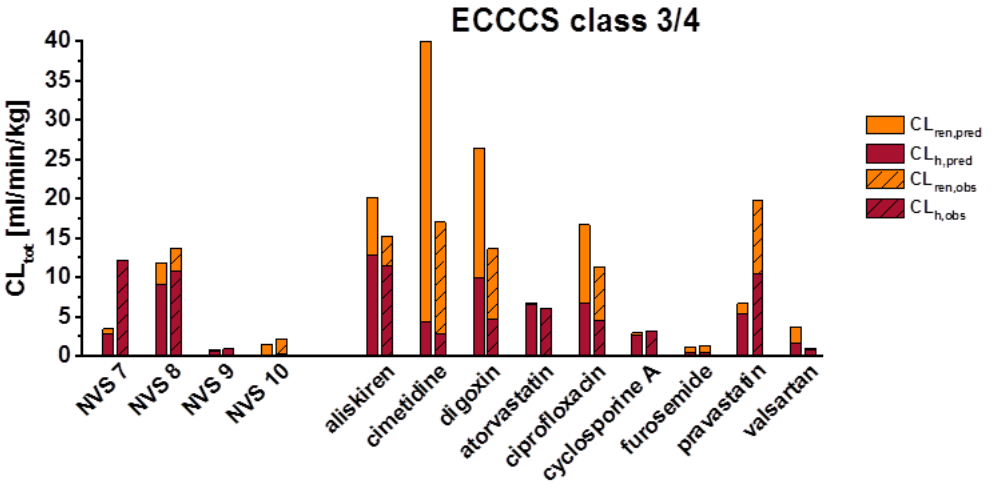
hepatic drug elimination

$$CL_{tot} = \frac{CL_h}{fn_h}$$



ECCCS class 3/4:

hepatic and **renal** drug elimination



→ **Accurate prediction of total drug clearance independent of elimination pathways**

Riede et al, 2016, Eur J Pharm Sci;86:96-102.

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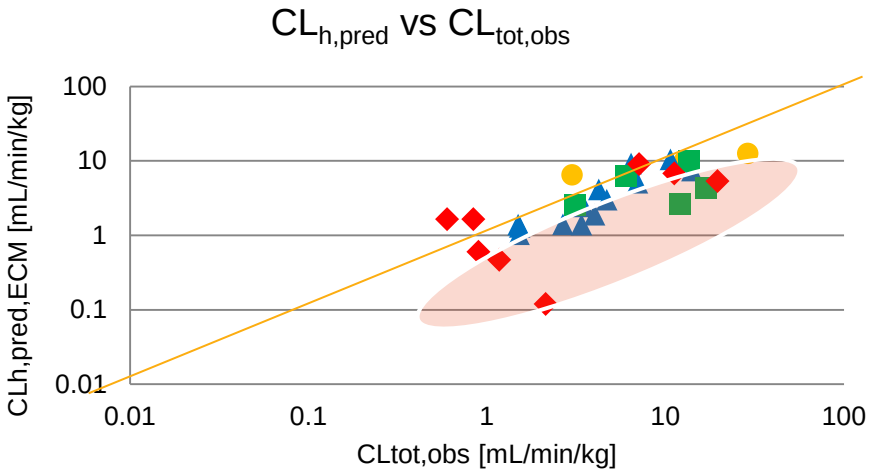
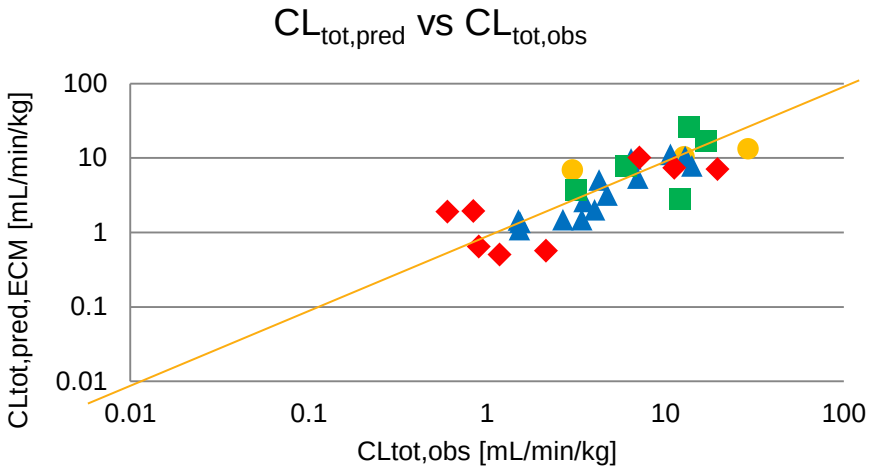
EC3S – Total Clearance IVIVE

Estimation of fractional hepatic elimination





Prediction of total human clearance

1) $f_{n,h}$ estimated from $PS_{inf,pas}$
2) CL_{tot} calculated with : $CL_{tot,pred} = CL_{h,pred} / f_{n,h,pred}$

(assuming absence of other elimination routes)

Riede et al, 2016, Eur J Pharm Sci;86:96-102.

Applications for drug classification

Guidance for the drug development process

- What is the recommendation with regards to metabolism investigations (*in vivo* or *in vitro*) ?
- What is the most appropriate clearance prediction tool for IVIVE?
- Are there opportunities to waive any animal studies (e.g. bile-duct cannulation studies)?
- What is the potential leverage with regards to in silico PK work?
- Is it recommended to synthesize a radiolabel in an early development phase?
- Which DDI follow-up studies (cpd as perpetrator vs victim) are recommended?

Applications for drug classification

	BDDCS	ECCS	EC3S
IVIVE		– Varma et al, Pharm Res (2015)	– Umehara and Camenisch, Pharm Res (2012) – Camenisch and Umehara, Biopharm Drug Dispo (2012) – Riede et al, Eur J Pharm Sci (2016)
Elimination Mechanism	– Hosey et al, The AAPS Journal (2016)	– Varma et al, Pharm Res (2015) – El Kattan et al, Pharm Res (2016)	– Riede et al, Eur J Pharm Sci (2016)
DDI	– Shugarts and Benet, Phar Res (2009)	– El Kattan et al, Pharm Res (2016)	– Kunze et al, Drug Metab Pers Ther (2015)
Kp_{uu}			– Riede et al, Drug Metab Dispos (2017)
Food effect	– Custodio et al, Adv Drug Deliv Rev (2008) – Himbach et al, The AAPS Journal (2012)		

Summary

- All compound classification systems provide information on drug disposition and the interplay between metabolic enzymes and transporters.
- ECCs and EC3S use *in vitro* data only. BDDCS requires information of a clinical dose and may therefore be positioned at a later stage in the drug development process.
- EC3S provides directly enables quantitative estimates of hepatic clearance and disposition processes given the required *in vitro* parameters are generated.
- All three classification systems may facilitate the compound class-dependent drug development process by guiding the selection of the most appropriate *in vitro* and *in vivo* studies

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Thank you for your attention

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